SEXUAL MEDICINE

WOMEN'S SEXUAL HEALTH

Peripheral Female Genital Arousal as Assessed by Thermography Following Topical Genital Application of Alprostadil vs Placebo Arousal Gel: A Proof-of-Principle Study Without Visual Sexual Stimulation

Sue W. Goldstein, BA, CCRC, IF,[1] Joshua R. Gonzalez, MD,[1] Catherine Gagnon, NP-C,[1] and Irwin Goldstein, MD[2]

ABSTRACT

Introduction: Female sexual arousal disorder is a pathophysiologic state characterized clinically by persistent or recurrent inability to attain or maintain an adequate lubrication-swelling response of sexual excitement until completion of sexual activity. Prior clinical experience with alprostadil products for men with erectile dysfunction supports its use in women with female sexual arousal disorder.

Aim: To compare the effect of topical alprostadil with over-the-counter (OTC) lubricant on female genital arousal in the absence of visual sexual stimuli.

Methods: Healthy premenopausal women without sexual dysfunction were recruited from the community to participate in the study. Of 17 women who consented, 10 were enrolled and completed the trial. The mean age of subjects was 32 years (range = 27–43). Study drug or placebo was applied topically to the genitals. Continuous temperature monitoring was performed. Participants completed questionnaires assessing genital sensation, effect, intensity, and duration.

Main Outcome Measures: Change in temperature from baseline in vestibule, clitoris and vulva.

Results: In all 10 subjects, topical alprostadil induced a statistically significant increase in temperature of the vestibule, clitoris, and vulva compared with the OTC lubricant. The most rapid difference in genital temperature between placebo and alprostadil was seen on the vulva, which demonstrated a significant difference at approximately 9 minutes. There was a significant difference in temperature seen for the vestibule and clitoris at 11 and 19 minutes, respectively. Sixty percent of women reported being aware or conscious of genital sensations with topical alprostadil, but not with OTC lubricant. Discordance was noted in 30% of subjects who reported being aware or conscious of genital sensations with the two treatments and 10% who reported not being aware or conscious of genital sensations with either treatment.

Conclusion: Topical alprostadil administered to healthy premenopausal women induced statistically significant, sustained increases in genital temperatures of the vestibule, clitoris, and vulva within 20 minutes compared with OTC lubricant.

Key Words: Female Sexual Arousal Disorder; Alprostadil; Thermography; Female Sexual Dysfunction; Genitals

INTRODUCTION

Female sexual dysfunction (FSD) is a multidisciplinary, biopsychosocial concern that can present with many distressing symptoms such as low sexual desire, decreased peripheral and/or central sexual arousal, orgasm dysfunction, and/or pain or discomfort during sexual activity.[1,2] The prevalence of overall FSD, independent of associated distress, has been estimated to be 43% of women.[3] The prevalence of FSD surpasses that of male sexual dysfunction.[4,5] Symptoms of FSD, when associated with distress, have been shown to negatively affect quality of life.[3]

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[1]San Diego Sexual Medicine, San Diego, CA, USA;

[2]Sexual Medicine, Alvarado Hospital, San Diego, CA, USA

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In women, physiologic sexual stimulation results in pelvic nerve-mediated genital smooth muscle relaxation and subsequent increases in hypogastric-pudendal arterial blood inflow. Initiation and maintenance of female sexual arousal consists, in part, of clitoral, vulvar, vestibular, and vaginal vasodilation, genital engorgement, and enhanced genital lubrication.[6,7] Female sexual arousal disorder (FSAD) is a pathophysiologic state characterized clinically by persistent or recurrent inability to attain or maintain an adequate lubrication-swelling response of sexual excitement until completion of sexual activity.[8] The prevalence of women with arousal complaints accompanied by distress is estimated to be 3% to 8% across all age groups.[1,9] Shifren et al[10] reported that the prevalence of distressing FSAD was 5.4%. Epidemiologic studies have shown that comorbidities of metabolic syndrome, such as obesity, diabetes, cardiovascular disease, and hypertension, can contribute to female genital arousal disorder.[11–17] Such comorbidities are associated, in part, with atherosclerotic lesions in the hypogastric-pudendal arterial bed that negatively restrict blood inflow increases to the peripheral genitalia during sexual arousal. Although the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* has suggested that FSAD should be linked to hypoactive sexual desire disorder (HSDD) in the entity "female sexual interest-arousal disorder," this remains controversial. The International Society for the Study of Women's Sexual Health and other societies have determined that the use of FSAD and HSDD as separate conditions should continue in clinical and research settings. The present research was performed in healthy women without sexual dysfunctions.

Prostaglandin E_1 (PGE1) naturally occurs in humans. PGE1 is a vasodilator that produces an increase in intracellular cyclic adenosine monophosphate and activation of protein kinase A. PGE1, unlike phosphodiesterase type 5 inhibitors (PDE5Is), increases blood flow without the need for sexual arousal. Increased protein kinase A activity has been shown to induce genital smooth muscle relaxation that in women can result in vulvovaginal vasodilation and enhanced genital lubrication, which are components of genital arousal.[6,7] Alprostadil is a vasoactive, synthetic form of PGE1 that has been approved worldwide for several intracavernosal and intraurethral products to treat erectile dysfunction.[18–21] Prior clinical experience with alprostadil products for men with erectile dysfunction supports its use in women with FSAD.[22–25] Several studies have examined the use of alprostadil in the treatment of FSAD, but effects on genital arousal from these previous investigations have largely been measured in a sexual context.[22–25] Becher et al[26] studied topical alprostadil on the clitoris alone using duplex Doppler sonography, but heretofore no one has studied the genital changes from application of alprostadil to the external genitalia compared with placebo. It is unknown whether topical alprostadil increases genital temperature (blood flow) and arousal without visual stimulation.

The objective of this proof-of-principle study was to evaluate the effect of a topical alprostadil cream (Femprox, Apricus Biosciences, Inc, San Diego, CA, USA) 1,000 μg on the external genitalia of sexually healthy women in the absence of sexual stimulus compared with an over-the-counter (OTC) marketed lubricant using forward-looking infrared (FLIR) thermography as a measurement of genital blood flow. The use of thermography as a method of measuring female sexual arousal has been well validated.[27–32] This was an investigator-initiated pilot study to determine whether a larger study in women with FSAD might be feasible. This novel study design was more rigorous than previous studies in its ability to assess genital blood flow changes in women using alprostadil. This single-blinded, placebo-controlled clinical trial used a non-invasive tool for measuring blood flow changes and timing of those changes without the confounding influence of sexual arousal in an office setting.

METHODS

Study Design

A prospective, randomized, single-center, single-blinded, crossover, proof-of-principle study was performed under independent review board approval. The study involved two counterbalanced crossover visits, each consisting of thermographic assessment of vestibular, clitoral region, and vulvar responses to non-sexual stimuli (ie, travel film) and completion of several self-report questionnaires. Alprostadil and placebo were randomized at the start of the trial and applied by an unblinded clinician who had no other involvement in the study, so that all other study procedures were performed and results were assessed in blinded fashion. The two visits of study drug application were scheduled with a washout (minimum = 1 day, maximum = 7 days) between visits.

Subjects

Healthy premenopausal women without sexual dysfunction were recruited from the community to participate in the study. The intention of the study was to enroll up to 15 subjects to obtain 10. Of 17 who consented, 10 were enrolled and completed the trial. The mean age of the subjects was 32 years (range = 27–43). Six subjects were Caucasian (five of whom identified as Hispanic), two were Pacific Islanders, one was Black, and 1 was East Asian. Only heterosexual women were included in the study.

Subjects had to be in good general health as determined by medical history, physical examination, and laboratory testing, have a normal body mass index (range = 20–30 kg/m^2), exhibit no clinically significant electrocardiographic abnormalities, have regular menstrual cycles (with not more than one missed menstrual period in the past 6 months), and be sexually active. All subjects were screened for pregnancy and were required to use a consistent form of contraception during the course of the study. Breastfeeding subjects were not allowed to participate.

Subjects were excluded if they did not meet all the inclusion criteria or had any musculoskeletal condition that would not allow