

the vaginal use of nonoxynol 9 in relation to dose, frequency of use, and the risk of becoming infected with STD/HIV.

Amaral et al. (Ref. 15) studied nonoxynol 9 in 18 women who were randomly and blindly assigned to an acid-buffering bioadhesive gel containing either 0 percent, 2.5 percent (125 mg), or 5 percent (250 mg) nonoxynol 9. Exclusion factors included a history of STD in the last 12 months, using any vaginal product within 7 days before admission to the study, or a known allergy to nonoxynol 9. Subjects were asked to abstain from sexual intercourse 48 hours before admission and during the study and not to use any other intravaginal products during the study. One dose of the assigned gel was administered vaginally daily for 6 days. No irritation or symptoms were reported by users of the acid-buffering bioadhesive gel without nonoxynol 9. Erythema in the vulva, cervix, and vagina was noted in all subjects using the acid-buffering vehicle containing nonoxynol 9 (2.5 percent and 5 percent). No signs of de-epithelialization or ulcers were seen in any of the subjects. However, the authors concluded that the acid-buffering vehicle did not protect the cervix, vagina, and vulva from the irritation caused by nonoxynol 9.

Stafford et al. (Ref. 16) studied the effects of daily use for 7 days of a nonoxynol 9 (100 mg) containing gel versus placebo gel in 40 women who were not currently using any intravaginal products, did not have a current STD, had no history of genital ulcerative disease, and were not known to be HIV seropositive. The subjects were asked to avoid sexual intercourse during the treatment period. The nonoxynol 9 group had increased symptoms of irritation. Colposcopic (use of a magnifying instrument) and histologic (microscopic) examination of vaginal and cervical tissue showed evidence of inflammation in the genital tract. Also, a temporary reduction in the number of lactobacilli (bacteria found in the normal vaginal flora that appear to offer protective effects against the overgrowth of certain organisms that cause infection) was seen more frequently in the women using the nonoxynol 9 gel.

Rosenstein et al. (Ref. 17) studied the effect on normal vaginal flora of three intravaginal microbicides (dextrin sulfate, nonoxynol 9, or docusate sodium, in a gel dosage form) in three separate placebo-controlled studies. In these studies, women using dextrin sulfate gel were asked to insert 5 milliliters of the gel intravaginally for 4

consecutive nights and women using nonoxynol 9 gel and docusate sodium gel were asked to insert the respective gels for 7 consecutive nights. A reduction of lactobacilli occurred in 56 percent of women who used nonoxynol 9 and 63 percent of women who used docusate sodium. Women using nonoxynol 9 were also significantly more likely to become colonized abnormally than those using placebo. It appeared that women were more likely to have their vaginal flora return to normal after nonoxynol 9 treatment if the lactobacilli had not been depleted. The authors expressed concern that continuous use of nonoxynol 9 would cause the vaginal flora to be altered persistently and, together with an increased risk of vaginal mucosal inflammation, could induce susceptibility to urinary and gynecological infection. The authors noted that it was essential that potential microbicides be examined for activity against normal vaginal flora.

In a single-blind crossover study of 33 women, Poindexter et al. (Ref. 18) compared three OTC vaginal spermicide formulations containing nonoxynol 9: A polycarophil-based gel with 50 mg of nonoxynol 9, a cellulose-based gel with 100 mg of nonoxynol 9, and a polyurethane sponge with 1,000 mg of nonoxynol 9. The subjects refrained from coitus for 3 days prior to and during the 7 consecutive days of the treatment period. There was a 21-day washout period between each treatment. New gynecological abnormalities occurred in all three groups using nonoxynol 9. Abnormalities observed included redness, white epithelium, ulceration, mosaic petechiae, and squamous metaplasia. Redness was the most common abnormality. Ulceration was noted in 2 of the 31 users of the nonoxynol 9 cellulose-based gel formulation. The authors noted that the abnormal effects of the vaginal spermicides were more profound on the cervical mucosa than the vulvo-vaginal mucosa.

Coggins et al. (Ref. 19) studied the safety of three vaginal spermicides containing nonoxynol 9: Film (70 mg), suppositories (150 mg), and gel (200 mg). Each woman used each product for a 4-week period and reported to the study center every 2 weeks. The authors did not indicate if there was a washout period between treatments. To avoid the potential for irritation from frequent use of nonoxynol 9 containing products, only women whose average coital frequency was one or fewer acts of intercourse per day were eligible to be enrolled. In this study, no ulcers or genital lesions were detected and

clinical signs of irritation were fairly uncommon and not frequent when compared to baseline. The authors concluded that these products are safe for low frequency use.

Watts et al. (Ref. 20) evaluated the effects of nonoxynol 9 on the vaginal flora and epithelium of 48 women (16 in each group) after application of a single dose and in the absence of sexual intercourse. Quantitative vaginal cultures and colposcopy were done at baseline and at 0.5, 4, 24, 48, and 72 hours after insertion of one of three commercially available vaginal spermicides containing nonoxynol 9 (200-mg gel, 52.5-mg gel, or 70-mg film). Symptoms and colposcopic abnormalities were rare after use of nonoxynol 9. The proportion of women with *Escherichia coli* (*E. coli*) increased with the gel containing 200 mg of nonoxynol 9 per dose and the concentration of *E. coli* increased with all of the test products. The authors noted that the transient decreased concentration of lactobacilli and increased levels of *E. coli* seen with all three test products are of concern and likely are intensified and perpetuated with repeated use of nonoxynol 9 as a microbicide. The authors suggested that adverse effects may be enhanced with frequent or chronic use and that chronic use may cause changes in the vaginal flora that may lead to urinary tract infection and other resultant complications.

Niruthisard et al. (Ref. 21) conducted a double-blind, local toxicity study on the effects of frequent use of nonoxynol 9 in 20 women who were not considered to be at high risk for STDs. Fifteen women used 150-mg nonoxynol 9 containing suppositories and 5 women used placebos (lubricating suppositories) inserted vaginally hourly for 4 consecutive hours each day for 14 consecutive days. The study concluded that none of the women who used the placebo suppositories had abnormal physical findings. Six women who used the nonoxynol 9 suppositories had physical findings, including epithelial disruption and/or bleeding. In four women, the break in the cervical epithelium appeared to be the result of the sloughing of a thin layer of cells. One woman had bleeding and sloughing of her vaginal mucosa and another had a severe reaction on her cervix that was bleeding and edematous. All of these adverse events resolved within 1 week of stopping nonoxynol 9 use. The authors cautioned that this pilot study should be confirmed by other trials and that these findings may not be extrapolated to other situations of nonoxynol 9 use.