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Cervicovaginal colposcopic lesions associated with five Nonoxynol-9 vaginal spermicide formulations

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Abstract

Objective—To compare the colposcopic appearance of the cervico-vaginal epithelium with spermicide use versus condom use in a low risk population.

Study Design—This was an ancillary study of a trial comparing the efficacy of 5 nonoxynol-9 (N-9) spermicides. A cohort of women using condoms without spermicide served as a control group. Colposcopic examinations were performed during product use to identify genital lesions.

Results—One hundred fifty-one participants had 1 follow-up examinations. At baseline, study groups differed only by the prevalence of baseline lesions. New lesions were identified at 49% of follow-up visits. Controlling for the presence of a baseline lesion, compared to condom use none of the spermicides were associated with an increase in new lesions (overall OR 0.8, 95% CI 0.4-1.6, $p=0.5$); and lesions characterized by epithelial disruption were less frequent with spermicide use (overall OR 0.3, 95% CI 0.1-0.6, $p<0.001$).

Conclusions—In a low risk population, women using N-9 spermicides were less likely to have lesions with epithelial disruption, and equally likely to have any new lesion compared to condom use.

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CONFLICT OF INTEREST

None

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Keywords

Colposcopy; vaginal spermicides; epithelial disruption; Nonoxynol-9

INTRODUCTION

Spermicides have been available in the United States (U.S.) for contraceptive use in a variety of formulations for almost half a century, and have significant differences from the two most popular reversible methods of contraception; oral contraceptives and condoms.²⁻⁴ Unlike oral contraceptives and other hormonal methods, spermicides are locally-acting with insignificant systemic effects or risk, and available over the counter. Unlike male condoms, vaginal spermicides are completely female-controlled. But similar to male condoms, they may decrease the transmission of certain sexually transmitted infections in addition to their contraceptive effects.⁵

One concern about spermicides is that the common active ingredient, nonoxynol-9 (N-9), may cause genital irritation that could increase the risk of transmission of sexually transmitted diseases.^{5, 6} Studies of women using N-9 containing spermicides frequently demonstrate genital irritation detected by colposcopy unrelated to symptoms.^{5, 7} Epithelial disruption, particularly deep disruption, may provide a route of access for HIV or other infectious agents. One study of frequent N-9 use by female commercial sex workers demonstrated an association between the presence of genital lesions and HIV transmission.⁶

In the past decade, colposcopic evaluation of the cervicovaginal epithelium has been used to systematically evaluate the safety of vaginal spermicide and microbicide products.⁸ The majority of these studies are not generalizable to low risk populations because they included only commercial sex workers, or evaluated frequent dosing (such as daily or more frequently) over a short period of time rather than typical coital use. Spermicide use with typical coital behavior represents less frequent exposure over a much longer period of time. To better understand the colposcopic appearance of the genital epithelium with typical long-term spermicide use, we performed this long-term study of low risk women using spermicides for contraception.

METHODS

This was an ancillary colposcopy study in a subset of participants in a multi-center randomized clinical trial comparing the contraceptive effectiveness of five N-9 spermicides. The primary study has been published previously.⁹ The present ancillary study was conducted at the University of Pittsburgh and the CONRAD Clinical Research Center at Eastern Virginia Medical School (EVMS). At EVMS, women planning to use male condoms for contraception were recruited as a non-randomized concurrent comparison group. The main and ancillary studies were approved by the Investigational Review Board at each Institution prior to subject recruitment. All participants provided written documentation of informed consent before participation in any study and prior to any study procedures.

Healthy volunteers at low risk for sexually transmitted infection (STI) were recruited from June 1998 to August 2002 for the main study.⁹ Participants of the main study and healthy controls at low risk for STI for the condom using group were eligible to participate in the colposcopy study if in addition to their eligibility for the main study, they: 1) had no recent history or evidence of a STI, 2) had not used spermicides or male condoms in the past 14 days, 3) had nothing per vagina for at least 72 hours prior to enrollment, 4) did not have any allergy or sensitivity to condoms or spermicides, and 5) were not menstruating at the screening visit. Participants were excluded if the investigator determined that any baseline lesions observed required medical follow-up or contraindicated intercourse or spermicide use.

Participants in the N-9 groups underwent all the procedures for the main trial, in addition to the visits and procedures for this ancillary colposcopy study, and participants in the group of condom users underwent the visits and procedures for the colposcopy study only. The genital epithelium was evaluated by colposcopic and naked eye examination at baseline and each follow-up visit (study weeks 4, 17, and 30). Examiners were not blinded to spermicide versus condom group assignment because the condom group was recruited as a cohort, but every attempt was made to blind examiners to spermicide assignment by participants and study staff. The World Health Organization (WHO) and CONRAD developed a standardized procedure, used for this study, specifically for evaluating vaginally administered products.^{8, 10} All lesions were recorded according to the standard classification system which defines lesions by the presence or absence of epithelial disruption and blood vessel disruption. (Table I) Additional descriptive information about the lesion, including location and size, was recorded systematically.

Before each examination, information was collected about coital and vaginal product use behaviors that might affect colposcopic findings. According to protocol, participants refrained from inserting anything into the vagina (other than study product with penile vaginal intercourse) for 72 hours before each colposcopy; and Papanicolou smears were collected at separate visits, 2 weeks before a colposcopy visit. If a lesion with bleeding, ulceration or global erythema was observed during examination, follow-up colposcopy was performed within 48-72 hours and thereafter until resolution. Observed lesions did not require discontinuation from the study unless cessation of intercourse or spermicide use was clinically necessary.

For the control group, participants were provided latex condoms with a silicone (non-spermicidal) lubricant. Participants in the spermicide groups were randomized after the baseline examination confirmed eligibility as previously described.⁹ Participants inserted a single dose of spermicide within one hour prior to each act of intercourse. Five spermicidal formulations containing N-9 were studied; 3 gels, a film and a suppository. The gels (A-C) represented increasing doses of N-9 in gel base packaged in prefilled single use vaginal applicators. Gel A (Advantage-24™, Columbia Laboratories, Inc., Miami FL) contains 52.5 mg N-9 at a concentration of 3.5% for each dose. Gel B (Ortho Options Conceptrol Gel®, Advanced Care Products, Skillman, NJ) contains 100 mg N-9 at a concentration of 4.0% per dose. Gel C is identical to Gel B, but each applicator was filled with a larger volume of gel for a total dose of 150 mg of N-9 per application. Each dose of film (Ortho Options

Contraceptive Film®, Advanced Care Products, Skillman, NJ), contained 100 mg N-9 at a concentration of 28% per sheet, measuring 6.35 × 6.5 cm. Each suppository (Encare®, Thompson Medical Company, Inc., West Palm Beach, FL) contained 100 mg N-9 at a concentration of 3.0% per dose. All products were packaged by the manufacturer as clinical trial material in packaging without a brand name.

The sample size was planned to include 30 participants in each study group to demonstrate a 50% difference in the prevalence of new lesions between groups. The primary analysis for this study was a descriptive evaluation of the prevalence of lesions among study groups at baseline and follow-up and a statistical comparison of the prevalence of new lesions between treatment groups. We categorized lesions by the presence or absence of epithelial disruption primarily and secondarily, by blood vessel disruption according to the CONRAD/WHO guidelines for colposcopic examination (Table I).¹⁰ All statistical analyses were performed using Stata® statistical software, release 9.1 (StataCorp, College Station, TX), and all statistical tests were evaluated at the 0.05 significance level. Differences in baseline characteristics of the women randomly assigned to the 5 spermicide formulations and the condom group were evaluated using analysis of variance or Pearson's Chi-square as appropriate. Generalized estimating equations (a statistical regression method for longitudinal evaluations) were used to identify factors that were associated with the prevalence of new colposcopic lesions observed after spermicide or condom use. Statistical inference was based on the generalized Wald test statistic.¹¹ Treatment-associated odds ratios for new lesions were adjusted for the presence of lesions detected at baseline (before treatment). The population averaged odds ratios derived from the generalized estimating equations models are presented along with the 95% confidence intervals and p values.

RESULTS

For the spermicide groups, 136 women from the main study enrolled in the planned colposcopy substudy, and an additional 31 women were recruited for the control (condom) group. Of the 167 women enrolled, 151 had at least one follow up visit that included a colposcopic examination and were included in this analysis. The demographic characteristics of the participants by study group are presented in Table II and were consistent with the main study.⁹ There were a few demographic differences among groups related to marital status and their primary method of contraception prior to enrollment. When the condom users were compared to spermicide users as one group, only the primary method of contraception prior to enrollment was significantly different. Condom users were more likely to use condoms (81% vs. 41%, $p<0.001$) and less likely to use withdrawal (6% vs. 35%, $p<0.001$) prior to enrollment than spermicide users. There were no other significant differences among demographic characteristics. The majority of participants had been treated for a vaginal infection at some time prior to enrollment (56%) but it was uncommon for participants to have been treated within 6 months of enrollment (10%). No urogenital or genital infections were noted at baseline, and related symptoms such as vaginal burning, itching or discharge each were rarely reported by participants (5%) at enrollment. Urogenital symptoms at baseline did not differ by treatment group, nor did condom users differ from spermicide users.

Coital behaviors and product exposure did not differ among treatment groups or between condom users and all spermicide users during the study. Participants reported a mean of 2.2 ± 1.3 coital acts per week ($p=0.6$) and a mean of 2.1 ± 1.3 episodes of product use per week ($p=0.5$). Coital behavior prior to examination was also similar among groups; the median number of coital acts in the week prior to examination was 2 (range 0-10, $p=0.8$) and the median days of abstinence prior to examination was 4 (range 1-244, $p=0.6$). The spermicide groups varied only by mean weekly exposure to N-9 ($p<0.001$) which was a direct result of the different doses of N-9 in each spermicide rather than any difference in product use behavior.

At baseline, 64 women (42%) had at least one lesion identified by colposcopy. The number of participants with at least one lesion (prevalence), the location and the size of those lesions all differed by treatment group at baseline (Table III). Compared to spermicide use, condom users were more likely to have a type A lesion ($p=0.001$) and less likely to have a type B lesion present at baseline ($p=0.001$). However, presence of a baseline lesion was not associated with any demographic characteristic. Participants in each group were followed for a similar amount of time (median 30 weeks, range 1-40 weeks). At follow up examinations, during spermicide or condom use, 333 lesions not present at baseline were documented, with descriptive data available for 307 new lesions. Thirty-six percent of new lesions were Type A and the level of epithelial disruption was graded as superficial (versus deep) for 91% (100/109) of Type A lesions. For all treatment groups, 2 lesions were described as deep epithelial disruption at a follow-up study visit. No lesion was described as having both epithelial and blood vessel disruption such as bleeding. Table IV describes the number of participant visits (follow-up) where at least one new genital lesion was identified.

Overall, there was no trend for use of any N-9 containing spermicide increasing the risk of any new colposcopic lesion compared to condom use, controlling for the presence of a baseline lesion. (Table V) Women using any spermicide formulation had fewer Type A lesions (epithelial disruption) compared to condom users (OR 0.3, 95% CI 0.1-0.6, $p=0.001$). In contrast, compared to condom users, women using any spermicide product were more likely to have lesions characterized by erythema or edema (Type C) (OR 12.5, 95% CI 1.7-91.8, $p=0.01$). The association was strongest for the suppository, which trended toward increasing the risk of a lesion for all lesion types except epithelial disruption. The N-9 suppository was the only spermicide associated with any increased risk of a new lesion by location or by gross visualization as compared to condom use. Compared to condom use, vaginal lesions were significantly less likely to be reported for all spermicide groups except for the suppository. Potential confounders such as study site did not affect the results. When controlling for the effect of location on type of lesion seen, the associations with product use remained the same.

DISCUSSION

In this study we describe the colposcopic genital findings in a low risk population of women, comparing the prevalence of epithelial lesions associated with long-term coital use of vaginal spermicides containing N-9 to latex condoms. Our findings are reassuring for this low risk population: compared to condom users, women using a spermicide were less likely

to have lesions with epithelial disruption than women using lubricated condoms without spermicide, and overall there was no consistent negative impact on the colposcopic appearance of the genital epithelium associated with spermicide use. This remained true when we considered separately each lesion type and each spermicide product, and controlled for the presence of a baseline lesion. Interestingly, only the vaginal suppository had any association with more new lesions than condom users, but not for lesions with disruption of the epithelium or blood vessels. This may be related to the use of a suppository rather than the spermicide; a similar association was reported in a study of a vaginal suppository containing antimicrobial agents.¹²

This study was strengthened by the inclusion of an appropriate control group. Although participants were randomized to the spermicide group they were not randomly allocated to the control group. It is possible that condom users had a higher prevalence of baseline lesions and an increased risk of new lesions of epithelial disruption because, as a group, they were more susceptible to lesions than the spermicide users. Controlling for baseline lesions did not change the results. In addition, with the exception of the presence of baseline lesions and the use of condoms as a primary method of contraception prior to enrollment, condom users were similar to the participants in the spermicide groups for all demographic characteristics and baseline findings. It is possible that the condom users were more susceptible to lesions for a yet unknown reason. However, it is also possible that condom use increases the susceptibility of lesions and condom users had a higher prevalence of baseline lesions because they were more likely to be using condoms prior to study enrollment. In addition, the condoms used were lubricated with silicone and the effect (positive or negative) of a lubricant used for condoms on the development of new lesions is unknown.

There was no standardization of exposure to product use because this was a trial of usual coital use, but we found no difference in behaviors that may have affected the outcome of interest, most notably coital activity and product exposure among the treatment groups. The treatment assignment was concealed until after randomization, and therefore the baseline colposcopic examination, to prevent selection bias. However, the participants and study staff were not blinded to the assigned spermicide group which could introduce bias in outcome ascertainment. Although every effort was made by study staff and participants to keep examiners blinded to spermicide assignment for this ancillary study, blinding to study group (condom use versus spermicide use) was not feasible because the control group was recruited as a cohort, and were not participants in the main trial. The primary outcome for the main study (contraceptive failure) and for this study (colposcopic lesions) used objective criteria for ascertainment and therefore less likely to introduce bias.

The clinical significance of colposcopically identified genital lesions is remains unclear. In a phase I trial of commercial sex workers using a vaginal film containing N-9 or placebo, the presence of *clinically* evident genital lesions was associated with increased HIV shedding.⁶ Asymptomatic genital lesions may be an important marker for safety but whether these lesions increase health risks is unknown. The type of genital lesion may be what determines the risk. Lesions characterized by deep epithelial disruption are of particular concern because epithelial integrity is lost but these lesions were rarely found in this study and were

not associated with spermicide use compared to condom use. Or it may be that other local effects, rather than epithelial lesions, determines health risk. Interestingly, in another sub-study of the main trial evaluating the change the vaginal flora associated with product use, N-9 product exposure was associated in a dose-dependent manner with an increased prevalence of vaginal microbes.¹³ No dose-dependent association was seen with dosing frequency or amount for genital lesions for this study.

While some studies have found a significant association between vaginal N-9 spermicide use and genital lesions, others have found none. The difficulty comparing studies is that the target populations have very different risks at baseline, may vary in exposure to the vaginal product, and may not have an appropriate comparison group as a control. Vaginal products containing N-9 were significantly associated with genital lesions in several studies of either high risk populations, or high exposure due to frequent administration or high doses of spermicide compared to placebo.^{5-7, 14} Even under these conditions, the associations are not consistent across studies.¹⁵ In other evaluations with greater exposure to the vaginal spermicide than expected from low risk coital use (i.e., more frequent use or higher doses), comparing different N-9 doses or products to each other or a placebo, no association between product use and genital lesions have been noted.¹⁶⁻²² Only one other investigation of a vaginal product containing N-9 was similar to this study; a low risk population, the coital use of the product, and follow-up over many months of use.²³ This study of two different formulations of the contraceptive sponge found no significant associations of product use with colposcopic genital lesions compared to baseline or between groups, similar to the present study. However, we were able to control for the effect of coital behavior by comparing vaginal spermicide use to condom use alone.

The evaluation of safety is paramount to the development and assessment of vaginal spermicides and microbicides because they are used as preventative medications, for contraception and/or prevention of sexually transmitted infections. Because these are female controlled and locally acting products, vaginal spermicides and microbicides will continue to be pursued worldwide to provide women the ability to control their fertility and prevent infections. Therefore the continued evaluation of the safety of vaginal products in the target population as preventive medications is as important as their efficacy.

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Table I

Categorization of colposcopic lesions by type of disruption (epithelial and/or blood vessels) and description.

Type	Epithelium	Blood Vessels	Description
A	Disrupted	Intact	Peeling, excoriation, laceration, fissure, abrasion, ulcer
B	Intact	Disrupted	Petechiae, ecchymoses
C	Intact	Intact	Erythema, hyperemia, edema
D	Not applicable	Not applicable	Other lesion not characterized by disruption of epithelium or blood vessel

Adapted from the CONRAD/WHO Manual of Standardization of Colposcopy for the Evaluation of Vaginally Administered Products, Update 2000.¹⁰

Table II

Demographic characteristics of study participants by study group^{*} presented by number and percentage (except as noted).

Characteristic	Condom (n=31)	Gel A (n=27)	Gel B (n=27)	Gel C (n=28)	Film (n=28)	Suppository (n=26)	p ^{**}
Age (Mean years $\pm$ standard deviation)	28.6 $\pm$ 2.7	27.0 $\pm$ 5.8	28.5 $\pm$ 6.4	28.7 $\pm$ 4.7	28.1 $\pm$ 5.2	27.9 $\pm$ 5.1	0.8
Race/Ethnicity							0.2
White, non-Hispanic	22 (71%)	24 (89%)	23 (85%)	19 (68%)	22 (79%)	24 (92%)	
Black, non-Hispanic	9 (29%)	2 (7%)	4 (15%)	7 (25%)	4 (14%)	1 (4%)	
Hispanic	0	1 (4%)	0	1 (4%)	0	0	
Other	0	0	0	1 (4%)	2 (7%)	1 (4%)	
Education							0.8
No degree	1 (3%)	1 (4%)	2 (7%)	0	1 (4%)	0	
High School/GED	14 (45%)	11 (41%)	8 (30%)	10 (36%)	12 (43%)	9 (35%)	
Associate Degree ($\leq$ 4 years college)	7 (23%)	7 (26%)	6 (22%)	7 (25%)	8 (29%)	7 (27%)	
College (4 years)	9 (29%)	5 (19%)	10 (37%)	9 (32%)	5 (18%)	6 (23%)	
Postgraduate	0	3 (11%)	1 (4%)	2 (7%)	2 (7%)	4 (15%)	
Marital Status							.03
Married, living with partner	18 (58%)	11 (41%)	14 (52%)	14 (50%)	18 (64%)	21 (81%)	
Single, living with partner	3 (10%)	11 (41%)	6 (22%)	10 (36%)	5 (18%)	3 (12%)	
Single, not living with partner	10 (32%)	5 (19%)	7 (26%)	4 (14%)	5 (18%)	2 (8%)	
Current Smoking (cigarettes per day)							0.3
None	28 (90%)	18 (67%)	19 (70%)	25 (89%)	20 (71%)	19 (73%)	
1 – 10	2 (6%)	4 (15%)	5 (19%)	3 (11%)	5 (18%)	5 (19%)	
11 or more	1 (3%)	5 (19%)	3 (11%)	0	3 (11%)	2 (8%)	
Obstetric History							0.4
Gravity							
0	6 (19%)	7 (26%)	7 (26%)	10 (36%)	7 (25%)	4 (15%)	
1	5 (16%)	7 (26%)	5 (19%)	7 (25%)	7 (25%)	8 (31%)	
2	14 (45%)	7 (26%)	11 (41%)	4 (14%)	4 (14%)	8 (31%)	
3 or more	6 (19%)	6 (22%)	4 (15%)	7 (25%)	10 (36%)	6 (23%)	
Parity							0.6
0	9 (29%)	10 (37%)	10 (37%)	13 (46%)	9 (32%)	7 (27%)	

Characteristic	Condom (n=31)	Gel A (n=27)	Gel B (n=27)	Gel C (n=28)	Film (n=28)	Suppository (n=26)	** p
1	8 (26%)	8 (30%)	7 (26%)	5 (18%)	7 (25%)	12 (46%)	
2 or more	14 (45%)	9 (33%)	10 (37%)	10 (36%)	12 (43%)	7 (27%)	

* Study Groups:

- Gel A: vaginal spermicide gel containing 52.5 mg N-9 per dose.
- Gel B: vaginal spermicide gel containing 100 mg N-9 per dose.
- Gel C: vaginal spermicide gel containing 150 mg N-9 per dose.
- Film: vaginal spermicide film containing 100 mg N-9 per dose (sheet).
- Suppository: vaginal spermicide suppository containing 100 mg N-9 per dose (suppository).
- Condom: male latex condom.

**
p = significance across study groups

Table III

Number (and percent) of participants with genital lesions seen at the baseline examination by study group.*

Lesions at Baseline	Condom (n=30)	Gel A (n=26)	Gel B (n=24)	Gel C (n=26)	Film (n=22)	Suppository (n=23)	p value**
All Lesions	14 (47%)	5 (19%)	12 (50%)	18 (69%)	6 (27%)	9 (39%)	0.006
Type of Lesion [†]							
Type A	11 (37%)	2 (8%)	2 (8%)	4 (15%)	0	1 (4%)	0.001
Type B	1 (3%)	0	4 (17%)	10 (38%)	3 (14%)	3 (13%)	0.001
Type C	0	1 (4%)	6 (25%)	4 (15%)	2 (9%)	4 (17%)	0.048
Type D	4 (13%)	3 (12%)	4 (17%)	6 (23%)	2 (9%)	3 (13%)	0.8
Location of Lesion							
Cervical	5 (17%)	4 (15%)	10 (42%)	16 (62%)	6 (27%)	7 (30%)	0.003
Vaginal	12 (40%)	1 (4%)	4 (17%)	6 (23%)	0	2 (9%)	0.001
External	0	1 (4%)	1 (4%)	3 (12%)	1 (4%)	1 (4%)	0.5
Visible Grossly	5 (17%)	2 (8%)	9 (38%)	14 (54%)	2 (9%)	6 (26%)	0.001
Size							
< 5mm	5 (17%)	1 (4%)	4 (17%)	12 (46%)	3 (14%)	7 (30%)	0.005
5 – 10mm	6 (20%)	3 (12%)	6 (25%)	5 (19%)	1 (4%)	2 (9%)	0.3
> 10mm	4 (13%)	2 (8%)	6 (25%)	7 (27%)	3 (14%)	2 (9%)	0.3
Global	1 (3%)	0	0	1 (4%)	0	1 (4%)	0.7

* Study Groups:

Gel A: vaginal spermicide gel containing 52.5 mg N-9 per dose.

Gel B: vaginal spermicide gel containing 100 mg N-9 per dose.

Gel C: vaginal spermicide gel containing 150 mg N-9 per dose.

Film: vaginal spermicide film containing 100 mg N-9 per dose (sheet).

Suppository: vaginal spermicide suppository containing 100 mg N-9 per dose (suppository).

Condom: male latex condom.

** p = significance across study groups.

[†] Lesion Type:

Type A: lesions with epithelial disruption

Type B: lesions with blood vessel disruption

Type C: lesions with neither epithelial nor blood vessel disruption

Type D: other lesions

Table IV

Number (and percent) of participant visits with new genital lesions seen at follow-up examinations by study group*

New Lesions at follow-up	Gel A (n=59)	Gel B (n=63)	Gel C (n=63)	Film (n=47)	Suppository (n=57)	Condom (n=76)
All	20 (34%)	32 (51%)	27 (43%)	22 (47%)	38 (67%)	39 (51%)
Type of Lesion**						
Type A	6 (10%)	9 (14%)	5 (8%)	5 (11%)	7 (12%)	28 (37%)
Type B	9 (15%)	10 (16%)	6 (10%)	9 (19%)	13 (23%)	7 (9%)
Type C	3 (5%)	11 (17%)	6 (10%)	9 (19%)	15 (26%)	1 (1%)
Type D	6 (10%)	2 (3%)	3 (5%)	1 (2%)	13 (23%)	5 (7%)
Location of Lesion						
Cervical	11 (19%)	16 (25%)	16 (25%)	16 (34%)	25 (44%)	15 (20%)
Vaginal	7 (12%)	9 (14%)	1 (2%)	5 (11%)	10 (18%)	26 (34%)
External	3 (5%)	3 (5%)	4 (6%)	3 (6%)	8 (14%)	4 (5%)
Visible Grossly	8 (14%)	16 (25%)	12 (19%)	15 (32%)	27 (47%)	13 (17%)

* Study Groups:

Gel A: vaginal spermicide gel containing 52.5 mg N-9 per dose.

Gel B: vaginal spermicide gel containing 100 mg N-9 per dose.

Gel C: vaginal spermicide gel containing 150 mg N-9 per dose.

Film: vaginal spermicide film containing 100 mg N-9 per dose (sheet).

Suppository: vaginal spermicide suppository containing 100 mg N-9 per dose (suppository).

Condom: male latex condom.

** Lesion Type:

Type A: lesions with epithelial disruption

Type B: lesions with blood vessel disruption

Type C: lesions with neither epithelial nor blood vessel disruption

Type D: other lesions

Adjusted* risk of new genital lesions by study group** and type of lesion*** after exposure to Nonoxynol-9 containing spermicide compared to condom use.

Table V

New Lesions at Follow up	Condom	Gel A	Gel B	Gel C	Film	Suppository
All	(Referent)	0.6 (0.3–1.4)	0.8 (0.3–2.1)	0.4 (0.2–1.1)	0.9 (0.3–2.3)	1.9 (0.7–4.8)
Type of Lesion						
Type A	---	0.3 [†]	0.4	0.2 [†]	0.3	0.3 [†]
	(Referent)	(0.1–0.8)	(0.1–1.1)	(0.04–0.7)	(0.1–1.1)	(0.1–0.9)
Type B	---	1.9	1.4	0.5	1.9	2.3
	(Referent)	(0.7–5.4)	(0.5–4.0)	(0.2–1.7)	(0.7–5.3)	(0.7–7.4)
Type C	---	4.0	14.6 [†]	7.5	16.9 [†]	25.6 [†]
	(Referent)	(0.4–37.5)	(1.8–116.4)	(0.8–65.9)	(2.2–129.6)	(3.2–208.0)
Type D	---	1.8	0.4	0.5	0.3	4.6 [†]
	(Referent)	(0.5–6.9)	(0.1–2.6)	(0.1–2.0)	(0.04–2.0)	(1.2–17.7)
Location of Lesion						
Cervical	---	1.0	1.0	0.8	1.8	2.6
	(Referent)	(0.4–2.5)	(0.4–2.7)	(0.3–2.3)	(0.7–4.5)	(1.0–7.2)
Vaginal	---	0.2 [†]	0.3 [†]	0.03 [†]	0.2 [†]	0.4
	(Referent)	(0.1–0.6)	(0.1–0.9)	(0.004–0.2)	(0.1–0.8)	(0.1–1.0)
External	---	0.9	0.9	1.0	1.1	2.7
	(Referent)	(0.2–4.2)	(0.2–3.7)	(0.2–5.1)	(0.3–4.6)	(0.8–9.2)
Visible Grossly	---	0.8	1.4	0.8	2.3	3.9 [†]
	(Referent)	(0.3–2.3)	(0.6–3.2)	(0.3–2.2)	(0.9–6.0)	(1.6–9.6)

* Adjusted for presence of type specific lesion at baseline. Risk of any new lesion adjusted for presence of any lesion at baseline, risk of new type A lesion adjusted for presence of type A lesion at baseline, etc.

** Study Groups:

Gel A: vaginal spermicide gel containing 52.5 mg N-9 per dose.

Gel B: vaginal spermicide gel containing 100 mg N-9 per dose.

Gel C: vaginal spermicide gel containing 150 mg N-9 per dose.

Film: vaginal spermicide film containing 100 mg N-9 per dose (sheet).
Suppository: vaginal spermicide suppository containing 100 mg N-9 per dose (suppository).
Condom: male latex condom.

Lesion Type:
Type A: lesions with epithelial disruption
Type B: lesions with blood vessel disruption
Type C: lesions with neither epithelial nor blood vessel disruption
Type D: other lesions

[†] p < 0.05