The safety of candidate vaginal microbicides since nonoxynol-9: a systematic review of published studies

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CRD summary
The authors concluded that larger and longer-term studies were required to detect clinically important toxicities of vaginal microbicides, including adverse effects that may be associated with a potential increase in HIV risk. Although there were limitations in the conduct of this review, the authors’ conclusions appeared to reflect limited evidence from small short-term studies and are likely to be reliable.

Authors' objectives
To evaluate the safety of vaginal microbicides other than nonoxynol-9.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched from inception to September 2008 for studies published in peer-reviewed journals. Reference lists were screened. Search terms were reported. Names of candidate microbicides were obtained from abstracts of Microbicides 2006 and 2008 conferences, Alliance for Microbicide Development website and reviews. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that evaluated microbicides other than nonoxynol-9 and reported safety outcomes other than HIV (human immunodeficiency virus) infection were eligible for inclusion. Studies were excluded if: the only control treatment was nonoxynol-9; treatments for genital infections were evaluated; only men were included; and if microbicide was used as a condom coating or with a diaphragm. Outcomes assessed in the review included genital signs with intact epithelium, genital signs with disrupted epithelium, urogenital symptoms, bacterial vaginosis, laboratory findings and other microbiology.

Included studies evaluated 11 different microbicides. The most commonly studied microbicides were cellulose sulphate, dextrin sulphate and Caraguard. Most studies used the vehicle produce as the control intervention. Median duration of interventions was 14 days (range five to 365). Exposure to microbicide lasted more than two weeks in only four studies. Participants were predominantly HIV-negative women; some studies included couples and HIV positive women. Studies were conducted in a variety of countries including USA and countries in Europe, Asia and Africa.

Two reviewers performed the searches. No further details of study selection methods were reported.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Where possible, numbers of events were extracted on a per protocol basis at end of treatment and used to calculate relative risks (RR) for each comparison; data included both drug-related and unrelated events. A continuity correction of 0.5 was added if there were no affected patients in either the treatment or control group. Studies with zero events in both treatment and control groups were excluded from analyses. Data for composite outcomes were included in analyses of the individual outcome measures. Within studies, multiple treatment with a common control group were treated as separate trials.

Two reviewers extracted data; it was not stated whether this was performed independently.

Methods of synthesis
Pooled relative risks with 95% confidence intervals (CIs) were calculated using a fixed-effect model in the absence of
significant statistical heterogeneity and the DerSimonian and Laird random-effects model where heterogeneity was present (p<0.1). Heterogeneity was assessed using Cochran’s Q statistic and the $I^2$ statistic.

**Results of the review**

Twenty-one RCTs were included (n=1,466 women). Median sample size was 59 (range 15 to 180). Confidence intervals were generally wide, which reflected the small sample sizes.

**Genital signs with disrupted epithelium (20 studies):** A statistically significant increase in genital signs with disrupted epithelium was found for UC781 (RR 5.75, 95% CI 1.05 to 31.39; one study, three comparisons, n=36 treated and 12 controls) and Savvy (RR 3.67, 95% CI 1.02 to 13.14; one study, n=40). There was no significant difference between any other treatment and control.

**Genital signs with intact epithelium (20 studies):** A statistically significant increase in genital signs with intact epithelium was found for PRO2000 (RR 1.69, 95% CI 1.08 to 2.60; two studies, three comparisons, n=60 treated and 37 controls). There was no significant difference between any other treatment and control.

**Urogenital symptoms (17 studies):** A statistically significant reduction in urogenital symptoms was found for UC781 (RR 0.46, 95% CI 0.23 to 0.94; one study, three comparisons, n=36 treated and 12 controls). There was no significant difference between any other treatment and control.

**Bacterial vaginosis (12 studies):** A statistically significant reduction in bacterial vaginosis was found for dextrin sulphate compared to placebo or no gel (RR 0.61, 95% CI 0.42 to 0.88; two studies, five comparisons, n=36 treated and control group size ranged from 15 to 37). There was no significant difference between any other treatment and control.

No heterogeneity was found for many of the above analyses.

**Laboratory parameters:** Four studies reported no laboratory toxicities. Five studies reported no significant difference between treatment and control.

Other microbiology findings were reported.

**Authors’ conclusions**

Larger and longer-term studies were required to detect clinically important toxicities of vaginal microbicides, including adverse effects that may be associated with a potential increase in HIV risk.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched. Attempts were made to minimise language bias, but not publication bias. Methods used to select studies and extract data were not described in full and so it was unclear whether adequate efforts were made to reduce reviewer errors and bias. Only RCTs were included, but study validity was not assessed and so results from these studies and any synthesis may not have been reliable. Studies were combined using meta-analyses. Heterogeneity was assessed. Where multiple treatment groups shared a common control group, no adjustment was made for statistical dependency; the authors acknowledged that this could have artificially reduced the confidence intervals. Some limitations of the evidence were discussed. Although there were limitations in the conduct of this review, the authors’ conclusions appeared to reflect limited evidence from small short-term studies and are likely to be reliable.

Several authors received funding for microbicide safety trials; they reported no conflict of interest. One reviewer had received grants from a number of pharmaceutical companies.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that larger and longer-term studies were required to detect clinically important toxicities.
on vaginal microbicides, including adverse effects that may be associated with an increased HIV risk. Such studies were required to provide assurance that microbicides were ready for large-scale trials of effectiveness. There was a need for researchers to develop standardised methods of designing and reporting safety trials.

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