Do spermicides containing nonoxynol-9 prevent sexually transmitted infections: a meta-analysis
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Authors' objectives
To systematically review and summarise the medical literature on the effect of spermicides containing nonoxynol-9 on the prevention of gonorrhoea, chlamydial infection and human immunodeficiency virus (HIV).

Searching
MEDLINE and AIDSLINE were searched for articles published between 1966 and July 1996 using the following keywords: 'vaginal creams, foams and jellies', 'contraceptive agents, female', 'nonoxynol' or 'spermicides' and either 'sexually transmitted diseases', 'HIV', 'gonorrhea' or 'chlamydia'.

Study selection
Study designs of evaluations included in the review
The review included clinical trials, cohort studies, case-control studies and cross-sectional studies.

Specific interventions included in the review
Interventions included in the review were nonoxynol-9-containing spermicides used separately from other barriers, such as condoms, diaphragms or cervical caps. The product formulations included sponge (n=3), film (n=1), gel (n=1), suppository (n=2) and cream (n=1). Three studies had no restriction on the product formulation. The dose of nonoxynol-9 ranged from 70 to 1000 mg.

Comparison groups included placebo (suppository or cream, lubricant or gel), tubal litigation, oral contraceptive pills, sterilisation, nonuser, low compliance, no contraception, no spermicide and nothing.

Participants included in the review
The participants were female commercial sex workers from Africa and Thailand, and women from clinics in North America. The mean sexual activity ranged from 34 partners per week to 1 per month.

Outcomes assessed in the review
Gonorrhoea, chlamydial infection and HIV were assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The quality of the randomised controlled trials (RCTs) was assessed by the presence or absence of five design characteristics: random allocation, blinding of treatment assignment, compliance assessment, measurement of confounding factors such as condom use, and loss to follow-up. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
Estimates of relative risk (RR) were calculated from results presented as odds ratios, risk ratios or hazard ratios. When several risk estimates were presented, the authors chose the one which was adjusted for confounding or the estimate in the study abstract. When 95% confidence intervals (CIs) were not presented, they were recalculated from the 90% CIs, variances, or other information in study articles. Study authors were contacted for additional information where CIs could not be determined.

In one study, information to determine CIs for gonorrhoea and chlamydial infection was not available. In this instance, the reviewers generated CIs for all possible 2x2 tables that conformed to the RRs and sample sizes provided, and selected the CI with the median width as being the most representative.

Pooled risk estimates were calculated for RCTs on gonorrhoea and chlamydial infection. The general variance-based method, which uses the fixed-effect model, was used. Outcomes were compared among studies using different spermicide delivery method, dose, compliance, sexual activity and setting.

How were differences between studies investigated?
The RRs and CIs for the RCTs were tested for heterogeneity.

Results of the review
Twelve studies (n=9,583) were included in the analysis: 6 RCTs (n=1,881) and 6 observational studies (n=7,702). The observational studies comprised 2 cohorts, 2 case-control and 2 cross-sectional studies. Three of the 12 studies evaluated the degree of protection according to consistency of use.

Heterogeneity tests were non significant (p=0.09 for gonorrhoea; p=0.99 for chlamydial infection).

The 11 studies evaluating gonorrhoea all found a reduced risk of infection with spermicide use. For the 6 clinical trials, the summary RR was 0.62 (95% CI: 0.49, 0.78), corresponding to a 38% reduction in gonorrhoea infections. Observational studies found an even greater degree of protection, with RRs ranging from 0.13 to 0.67. The absolute risk differences ranged from 2 to 6 fewer cases per 100 woman-months in public health clinics, and 8 to 20 fewer cases per 100 woman-months among prostitutes.

Each of the 5 studies of chlamydial infection also found fewer infections among women using spermicides. The pooled risk estimate among the 4 clinical trials was 0.75 (95% CI: 0.62, 0.91), corresponding to a 25% reduction in chlamydial infections. The single observational study found a similar reduction in chlamydial infection (RR=0.67). Absolute risk differences ranged from 2 fewer cases per 100 woman-months in a public health clinic setting, to 14 fewer cases per 100 woman-months in a study among prostitutes.

In each of the 3 studies evaluating the effect of consistency of spermicide use, more consistent use was associated with stronger protection against gonorrhoea and chlamydial infection. There were no systematic differences in clinical outcomes according to spermicide delivery method, dose, sexual activity or study location. However, the small number of studies limited such comparisons.

Two studies investigated the association between spermicide use and HIV infection. The clinical trial found a non significantly increased risk (RR 1.7, 95% CI: 0.9, 3.0), whilst the observational study found that more consistent spermicide users experienced a protective effect against HIV (adjusted RR 0.1, 95% CI: 0.1, 0.6).

Authors’ conclusions
Spermicides containing nonoxynol-9 had a protective effect against gonorrhoea and chlamydial infection. There were insufficient evidence to judge their effect on HIV transmission.

CRD commentary
The authors clearly stated the inclusion criteria. Details of the included studies were summarised clearly in tabular format, and the quality of each study was discussed. The data synthesis was clear and well presented.
The authors searched MEDLINE and AIDSLINE over a period of 30 years. The search could also have included a search of EMBASE, an attempt to identify unpublished studies, and a handsearch of journals. There was no mention as to whether the search was limited to articles published in the English language, so the risk of publication bias cannot be ruled out.

The quality of each RCT was assessed by the presence or absence of five important design characteristics, although it was unclear whether the studies had to meet all five characteristics to be eligible for inclusion in the systematic review. The authors did not link the quality of the RCTs with interpreting the data or the meta-analysis. No attempt was made to assess the quality of the observational studies.

The length of the follow-up period was not stated. In addition, there was no indication as to whether the data were extracted in an intention to treat format, or whether the studies were weighted prior to combination.

The authors state that a heterogeneity value (p) of 0.09 for studies investigating an outcome of gonorrhoea is non significant. However, due to the underpowered nature of heterogeneity tests, it is questionable whether one could conclude that the studies are homogeneous.

The authors' conclusions follow logically from the results presented.

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

The authors stated that further research on the effect of nonoxynol-9-containing spermicides on HIV transmission is urgently required, so that evidence-based clinical decisions and public health recommendations can be made in the future. Future research should also investigate whether high doses or frequent use of nonoxynol-9 cause ulceration or damage to genital epithelium. It is also unclear whether product formulations alter the preventative effect of nonoxynol-9. Future research investigating the best formulation should also explore cost, ease of use, and consumer practice.

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