

Discussion: 'Douching and the risk for sexually transmitted disease' by Tsai et al

In the roundtable that follows, clinicians discuss a study published in this issue of the Journal in light of its methodology, relevance to practice, and implications for future research. Article discussed:

Tsai CS, Shepherd BE, Vermund SH. Does douching increase risk for sexually transmitted infections? A prospective study in high-risk adolescents. *Am J Obstet Gynecol* 2009;200:38.e1-38.e8.

DISCUSSION QUESTIONS

- What are the main objectives of this study?
- How were sexually transmitted infections (STI) detected?
- How was information on douching collected and described?
- What are the primary findings of the study?
- What are the strengths and limitations of each survival analysis?
- Why use 2 approaches to estimate time to incident STI?
- Why is the odds ratio for incident STI not consistent with survival analysis data?
- How generalizable are the findings?

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INTRODUCTION

Of the 7643 women, aged 15-44 years, who were interviewed for the 2002 National Survey of Family Growth, 32.2% had douched in the 12 months prior to the survey. Although the practice was generally less prevalent among participants aged 15-19 years (15.7%), it was far more common among non-Hispanic black adolescents: 32.8% versus 11.2% of Hispanic or Latina adolescents and 13.3% of white subjects. Douching has been connected with bacterial vaginosis (BV), sexually transmitted infections (STIs), and pelvic inflammatory disease. The study by Tsai and colleagues examines the role of douching on incident STIs among human immunodeficiency virus (HIV)-positive and HIV-negative adolescents with high-risk sexual behaviors.

*Jenifer E. Allsworth, PhD and
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STUDY DESIGN

Allsworth: *What are the main objectives of this study? Are these important questions to study?*

Rohn: This study aimed to investigate whether douching was associated with an increased risk of STI incidence in adolescent females. Particularly, what is the association among teens who are infected with HIV? I believe this is an important question.

Douching is common, with estimates of about a quarter of women engaging in the practice. Its prevalence is higher among minority women and women who engage in high-risk sexual behaviors. Moreover, the practice is often initiated during adolescence, making this an important time for potential inter-

vention. Reports indicate that women are less likely to douche if they have been informed by a healthcare provider that douching is not recommended. Not only is douching medically unnecessary, it has, in fact, been linked to multiple adverse outcomes. Some evidence suggests that douching might increase STI risk, but few prospective studies have been published. If douching was found to raise the risk for STIs, the data could create an opportunity to reduce rates of infection by counseling women to avoid the practice.

Allsworth: *The study design is a matched prospective study. Can you describe the study design and discuss why matching was deemed necessary in this study?*

McNicholas: This study used a subset population from the Reaching for Excellence in Adolescent Care and Health (REACH) Project of the Adolescent Medicine HIV/AIDS Research Network. That study originally enrolled adolescents, aged 12-18 years. A portion of the population was infected with HIV. Inclusion criteria required that the adolescents agree to obtain primary care and that some form of medical care payment was in place. A further stipulation was that HIV-positive patients were to have acquired the infection through drug use or sexual behavior.

The specific subset that made up the population studied by Tsai and colleagues was restricted to females, aged 12-19 years. In an effort to isolate the effects of HIV, this group was matched to a control group of HIV-seronegative females of similar age, race, ethnicity, and sexual and drug-use behaviors. Because HIV is rare in this age group, these teens and their demographics needed to be

identified before an adequate control group could be assembled.

Allsworth: *This paper looked at 4 STIs: Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae, and herpes simplex virus (HSV) type 2. How were these detected?*

Hotchkiss: *C. trachomatis* and *N. gonorrhoeae* were detected using the ligase chain reaction technique on first void urine, anal swab, and endocervical samples. *Trichomonas vaginalis* was detected using warm saline wet mount samples, culture, and cytology, but clear identification on any of the 3 was considered diagnostic of an infection. Finally, HSV-2 was detected by serologic testing with a validated in-house enzyme-linked immunoassay.

Allsworth: *The authors describe 3 different tests for the detection of trichomoniasis. Why do you think multiple tests were used?*

Hotchkiss: There are multiple ways of diagnosing trichomoniasis, and these vary greatly in sensitivity and cost. Wet mount reveals the presence of motile trichomonads in only 50-70% of culture-confirmed cases, and the organisms only remain motile for 10 to 20 minutes after collection of the sample. The sensitivity of cytologic diagnosis is low, around 60%, but specificity is 99%, with a low false-positive rate. Generally, it is not used as a primary means of detecting trichomoniasis infection at times when a Papanicolaou smear is not needed. Culture has a high sensitivity (95 percent) and specificity (>95 percent), and it should be considered when a high suspicion for infection exists but wet mount proves nondiagnostic.

Allsworth: *How was information on douching collected and described? Are there important aspects of douching behavior that may have been missed in this definition?*

Rohn: Data on douching was collected from Audio Computer-Assisted Self-Administered Interviews, in which participants answered “yes” or “no” to a question on whether or not they douched. The specific wording of the question was not provided in the paper. Subjects who answered “yes” at each study visit were classified as always

douching; subjects who answered “no” at each visit were classified as never douching; and subjects who answered differently at different times were categorized as women who douche intermittently. Several important aspects of douching behavior were not captured; for example, douche products used, technique, reasons for douching (eg, following menses, itching, new or multiple sex partners, odor), and frequency of douching. The lack of frequency data suggests the possibility that the always and intermittent douching categories might each represent heterogeneous groups, including women who douched rarely or in response to symptoms, as well as those who douche regularly. [Wouldn't this be particularly true of the always group, since they were answering yes at every visit?]

STATISTICAL ANALYSES

Allsworth: *What are the primary findings of the study?*

Rohn: The study found that the time to STI (measured from the first STI-free study visit) was shorter for those who always douched (hazard ratio or HR, 2.1; 95% confidence interval or CI, 1.2-3.4; $p=0.007$) and for those who intermittently douched (HR, 1.5; 95% CI, 1.0-2.2; $p=0.05$). When adjusted for HIV status, race, baseline sexual activity, and age, the hazard ratio was 1.8 (95% CI, 1.1-3.1; $p=0.02$) for those who always douched and 1.4 (95% CI, 0.9-2.0; $p=0.13$) for patients who intermittently douched. The authors also performed this analysis on the subset of patients who entered the study STI-free, and they got similar results.

Another analysis used only information gathered from STI-free study visits to classify subjects as never, intermittent, or always douching. The time to STI was, again, shorter for those who always douched, with an adjusted HR of 2.1 (95% CI, 1.5-3.1) for all subjects and an adjusted HR of 2.5 (95% CI, 1.6-3.9) for the subset who entered the study without an STI.

In addition, the authors looked at whether a report of douching at the current visit was predictive of STI. They

found that a report at the current visit of having douched in prior months was associated with STI at the current visit (OR, 1.3; 95% CI, 1.0-1.6), as well as an STI at the next 6-month visit (OR, 1.3; 95% CI, 0.98-1.7). After adjusting for existence of STI at the current visit, a report of douching at the current visit was still associated with an STI at the next visit (OR, 1.3; 95% CI, 1.0-1.7). When adjusted for baseline HIV status, age, and race, the association between a current report of douching and an STI at the next visit was not statistically significant (OR, 1.2; 95% CI, 0.9-1.6; $p=0.2$).

Allsworth: *The authors use 2 types of survival analysis: the Kaplan-Meier curve and Cox proportional hazards regression. Can you tell us what each is used for and its strengths and limitations?*

Hladky: Survival analysis is a statistical method to describe a time-to-event. Kaplan-Meier curves and Cox proportional hazards are 2 forms of survival analyses. Kaplan Meier curves are used to show time-to-event, with intervals generated each time an event occurs. They can be used to calculate a cumulative probability of survival (eg, absence of the event). Strengths of the Kaplan-Meier curve include an ability to allow comparison of “survival” between groups. The test is limited by assumptions that there are no changes in confounding variables over the length of the study period and that the event of interest may only happen (or be analyzed) once. So in this study, it's important to realize that the Kaplan-Meier curve assumes there are no interventions and no changes occurring in this cohort of patients during the follow-up period.

The Cox proportional hazards regression is used to determine the hazard ratio or risk of event at specific times while adjusting for covariates. One limitation is the assumption that variables will not change with time (ie, time-independent variables). If variables are time-dependent, additional testing or stratifying of data is required.

Allsworth: *The analyses focus on 2 approaches to estimating time to incident STI. Can you explain why this*

was necessary? What are the strengths and limitations of each approach?

Hladky: The authors describe 2 approaches to evaluate time to incident STI by multivariable Cox proportional hazards regression. In the first analysis, they investigated the association between douching behavior throughout the follow-up period on the time to development of STI, using the participant's first STI-free visit as "time-zero." So if the patient entered the study with an STI, researchers waited until the first visit where the patient did not have an STI. In the second analysis, they evaluated the relationship between the douching behavior reported only for an STI-free interval and the time to STI occurrence.

The first analysis reports overall behavior, taking into account douching behavior when the subject may have an STI. A potential limitation is confounding if douching was a result of STI symptoms (eg, the participant douches because of vaginal itching). This analysis found a significant association between douching patterns and STI.

The second analysis focuses only on douching behavior during intervals when, at the start of the interval, the subject is known to be STI-free. This limits the potential bias of douching due to STI symptoms. However, this approach may overestimate the number of patients categorized as using "intermittent douching," given that as subjects remained in the study, they were more likely to enter this category. That is, this group could have become overinflated if a large number of women who stayed in the study and remained STI-free for an extended period reported that they had douched at some point in the course of the investigation. Members of this group might actually have minimal exposure to douching; for example, douching once or twice during the research.

Allsworth: *In Table 3, the adjusted odds ratio for incident STI is presented, and there is no significant association with douching. Can you explain this inconsistency with the findings from the survival analyses?*

Hladky: Table 3 analyzes the association between douching behavior at any STI-free visit and the likelihood of devel-

oping of an STI at the following visit. This analysis allowed for multiple outcome analyses for each subject. After adjusting for significant variables, including baseline HIV status, age, and race, the relationship between douching and STI development was not significant. These results probably differ from the survival analysis data because a short period of time was analyzed. Perhaps the analysis was underpowered to detect a difference in STI rates over just 6 months.

Allsworth: *The multivariable models adjust for baseline age, race, baseline HIV status, and whether or not the participant had sex in the last 3 months before the baseline interview. Are there additional factors that you think are important to consider?*

Hotchkiss: It is also important to consider the number of sexual partners that participants had; whether partners of women positive for an STI received treatment; the presence of BV; the use of barrier or hormonal contraception; and the level of immunocompromise in HIV-infected participants. All of these factors could affect the patient's likelihood of acquiring an STI. You could also adjust for socioeconomic status and level of education.

Allsworth: *The authors have excluded BV as a potential outcome of interest due to concerns about its very high prevalence. Do you think they provided adequate justification for this? How might this impact study results?*

McNicholas: BV is highly prevalent and may be an important modifier of the relationship between douching and STI, so I do not think that its exclusion as an outcome was justified sufficiently. One of the consequences of frequent douching might be BV. By ignoring patients with BV, the researchers might have masked a possible relationship between the incidence of BV and concurrent STIs. If they wanted to exclude BV from the outcomes, they should have added consideration for that in the multivariable analysis or completely excluded patients with BV.

Allsworth: *The authors mention a median of 3 years of follow-up for their*

participants. Why is length of follow-up such an important issue in prospective studies?

Hotchkiss: A prospective study follows a cohort for outcomes, such as the development of a disease, and relates this to other factors, such as suspected risk or possible protective factors. The study usually involves taking a cohort of subjects and watching them over a long period. When a cohort is followed for a longer time, more precise information about the causality of the outcome and the risk/protective factors can be gathered. As researchers, we are concerned about length of follow-up because differential dropout can bias study findings. If women who reported douching and who were at the highest risk for STI acquisition were also more likely to drop out quickly, this could lead to an underestimation of the true association. However, as the authors reported, the annual retention rate in this study was excellent—95% for HIV-infected adolescents; 88% for non-HIV-infected adolescents—so concern about bias is minimized.

Allsworth: *In Figure 3, intermittent douching appears to have a beneficial impact compared to never douching, but the authors believe this to be an artifact. What was their explanation for this finding? Do you agree with their conclusion that this estimate is likely biased?*

McNicholas: The authors attributed this to an artifact of categorization. They proposed that over a longer follow-up time, a greater proportion of participants would fall into the intermittent douching group. However, in the conclusion of the paper, the authors referred to the intermittent category as a methodological concern, citing too much diversity within the group. If their first claim is true, that over time, a greater proportion of woman will fall into the intermittent category, it would seem that the more clinically relevant group would be the intermittent group. Furthermore, considering the limited number of prospective studies of this issue, most of which have produced conflicting results, the proposed explanation was not sufficient.

CONCLUSIONS

Allsworth: *Data collection for this study began in 1996. Are there trends in adolescent STIs that might impact the interpretation and generalizability of these findings?*

Rohn: According to the most recent Centers for Disease Control and Prevention (CDC) report, *Trends in Reportable Sexually Transmitted Diseases in the United States, 2006*, the incidence of gonorrhea declined 74% from 1975 to 1997, and then reached a plateau, with a small increase in 2005 and 2006. In contrast, the rate of chlamydia infection increased over 6-fold from 1987 through 2006. Although part of this increase is likely due to increased screening and use of more sensitive tests, the true incidence of chlamydia may have increased as well. The highest rates of both diseases continue to be seen among adolescents. Based on CDC reports, it does not appear that rates of either gonorrhea or chlamydia among adolescents have drastically changed since the mid-nineties. However, there are variations in prevalence among different subgroups; African American women are disproportionately affected by both chlamydia and gonorrhea, and gonorrhea is more common in the southern United States. In

this study, high-risk adolescents were well represented. This may affect generalizability to other groups, as might the fact that douching is more prevalent among high-risk women.

Allsworth: *Do you think that the cohort in this study is representative of the clinical populations you see? How would the inclusion criteria that only adolescents enrolled in a comprehensive, adolescent-specific medical care center enhance or limit generalizability?*

McNicholas: The race, ethnicity, health insurance coverage, and other social variables of the study population were similar to those of the teens seen at our urban, university-affiliated clinic. And although we do see a good number of older adolescents, aged 17-18 years, it is not an overwhelming proportion of our patients. Of the adolescents I do see, very few are HIV-positive. The behavioral variables of this cohort were also not reflective of my patient population. For example, in the HIV-positive group, 45% reported more than 8 partners—as did 25% of the HIV-negative participants.

The exclusion of older age groups and the requirement to be enrolled in a medical care center definitely reduce the generalizability. Individuals enrolled at a

medical center may be at lower risk for STI and have more access to medical information on the consequences of douching. But, despite this reduction in generalizability, these findings do represent a high-risk cohort and will be informative for clinicians counseling their patients.

Allsworth: *The authors recommend strongly that public health action is needed to educate young females about the health risks associated with douching. Do you agree with this recommendation?*

Hladky: This study provides some of the only prospective data suggesting that douching may be a causative factor in STI acquisition. However, the adjusted odds ratio when using douching behavior to predict STI at the next study visit was not statistically significant. Also, as the authors note, the study methodology used to assess details of douching behavior does have limitations, and the high-risk nature of the study population of teenagers, many of whom have HIV, limits generalizability. This study's findings support the need for further, definitive research. While we have good evidence to suggest douching is not beneficial, it is too soon to advocate a significant change in public health education without further prospective research. ■