

Risk Factors for Development of Toxic Shock Syndrome

Association With a Tampon Brand

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• In September 1980, we interviewed by telephone 50 patients with menstrually associated toxic shock syndrome (TSS) who had onset of illness in July or August 1980. These women were asked to provide information about the type of menstrual sanitary products used during the menstrual period associated with their illness. We also interviewed 150 age-matched control subjects, who were asked the same questions for the menstrual period that occurred in the same month as the illness of the matched case. All 50 cases, but only 125 of 150 controls, used tampons. Among women using tampons, cases were more likely to have used Rely® brand tampons when compared with controls. No differences were found between cases and controls in the absorbency of tampon products used. No other factors studied through analysis of a follow-up questionnaire mailed five months after the first study were found to be significantly associated with the development of menstrually associated TSS.

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TOXIC shock syndrome (TSS) is a recently described illness primarily affecting menstruating women and characterized by fever, hypotension, diffuse erythroderma, desquamation, and impairment of multiple organ

See also pp 840 and 872.

systems.¹⁻³ Toxic shock syndrome has been strongly associated with infection with or carriage of strains of *Staphylococcus aureus* capable of pro-

ducing exotoxin(s) with pyrogenic⁴ and enterotoxic properties.⁵ A case-fatality rate of 5.6% has been seen in cases reported to the Centers for Disease Control (CDC).⁶

Previous case-control studies of TSS in menstruating women done by the CDC and in Wisconsin established a link between this illness and the use of tampons, particularly continuous use, during the menstrual period.^{2,3} These studies did not establish an association between a particular brand of tampon and TSS. The first case-control study performed at the CDC in June 1980, however, may have masked such a difference, as cases were asked to provide information about menstrual devices used before an illness that occurred up to several years before the study, while controls

were questioned about the use of menstrual devices during their most recent period. Because of the introduction of many new tampon products in the late 1970s, tampon products available to control subjects were not equally available to cases for the menstrual period for which these data were obtained. Despite this bias, the greatest percentage of cases in the first CDC study reported using Rely® brand tampons, a product introduced into the tampon market in 1978 (Fig 1). We therefore performed another case-control study in September 1980 to test the hypothesis that one or more brands of tampons might be more strongly associated with TSS than other brands.

SUBJECTS AND METHODS

Case Selection and Case Interviews

All cases of female patients with TSS reported to the CDC who had onset of illness in July or August 1980, who survived their illness, and who met a strict case definition⁷ were eligible for the study. Fifty cases meeting these criteria had been reported by the first week in September, and all these women agreed to participate in the investigation.

Each of these women was contacted by telephone, and a short questionnaire was administered. Age, race, and approximate family income were established; each woman was then asked about the type of menstrual device used during the period associated with her recent illness. Women who used tampons were asked to provide

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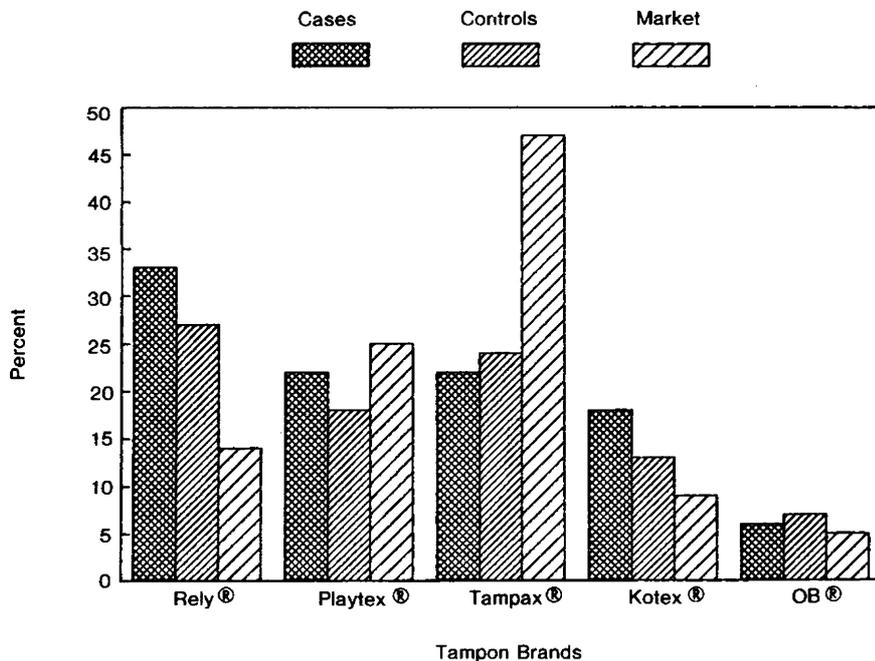


Fig 1.—Distribution of tampons brands used by participants in Centers for Disease Control case-control study, single-brand users only, June 1980.² Market data were estimates supplied by manufacturers of share of tampon market held by their products in June 1980.

the brand name and absorbency of each tampon used, as well as the number of tampons used each day during the menstrual period. Each participant was asked to examine her tampon box and read the label to the interviewer. In addition, all women were also asked whether tampons were used on any nonmenstrual day, whether more than one tampon was used at a time, and whether they had changed their brand or absorbency of tampon for the period associated with their illness. Interviews were conducted in a uniform manner by physicians of the Toxic Shock Syndrome Task Force and General Epidemiology Branch, Bacterial Diseases Division, Center for Infectious Diseases.

Control Selection and Control Interviews

Cases were asked to provide the names of three friends or acquaintances of the same sex who lived in the same geographic area and were within three years of her age. In some instances, the women could provide only two acquaintances to serve as controls; in other instances, four controls were identified for each case.

For any individual case, each control was contacted by the same interviewers and administered the same questionnaire used for case interviews. Control subjects provided information about the menstrual period that occurred the same month in which the case became ill. In a few instances, however, cases had become ill before the onset of the control subject's period for that month, and the control had

changed her use of menstrual device because of this. Information about the use of menstrual devices was then obtained for the preceding month. All interviews of cases and control subjects were completed during the second week of September 1980.

Follow-up Survey

In February 1981, five months after completion of the initial case-control interviews, an expanded questionnaire was mailed to study participants. It was designed to assess additional risk factors for TSS and changes in the use of tampons among cases and control subjects after release of information from the first part of the study. Detailed information was gathered about socioeconomic status, crowding in the home, previous medical history and contact with health care providers, use of medications, methods of birth control, sexual practices, and personal hygienic practices.

Statistical Analysis

Differences between cases and controls for tampon use and tampon brand use were analyzed using the Pike-Morrow extension of the Mantel-Haenszel test for multiple matched controls per case.⁷ Relative risks and 99% confidence intervals were calculated for each variable.

A linear logistic regression model for matched case-control studies was used to estimate multiple relative risk functions in determining the importance of brand and absorbency as discrete and continuous

risk factors in a multivariate model.⁸

Statistical analyses of the follow-up survey used Fisher's exact tests because cases and controls participating were unmatched to ensure the confidentiality of their responses.

RESULTS

Telephone Survey

Fifty cases and 150 control subjects were contacted. All 50 cases and 125 of 150 controls used tampons during the menstrual period of July or August 1980. Case-control triplets, quadruplets, and quintuplets for this analysis are presented in Fig 2. The difference in tampon use between cases and controls was significant ($P < .01$).

Forty-two of the 50 cases were exclusive users of a single brand of tampon during the menstrual period associated with their illness; 113 of their matched controls were exclusive users of a single brand during the corresponding menstrual period. The distribution of tampon brands for these exclusive users is given in Table 1. The matched analysis of the distribution of Rely brand tampons between cases and controls is shown in Fig 3. Cases were more likely than controls to have used Rely brand tampons ($P < .0001$). The relative risk for the development of TSS for those who used Rely compared with the risk associated with using other tampon brands was 7.7 (99% confidence intervals, 2.1 to 27.9). Similar differences were seen when preponderant use of a single brand of tampon and any use of a single brand of tampon were analyzed for the matching menstrual periods. No increased risk was demonstrated for any other brand of tampon used by cases and control subjects in the study; confidence intervals for other tampon brands encompass 1.0 (Table 2). However, the smaller number of non-Rely users among cases¹² precludes accurate estimates of risk among other tampon brands.

Increased and preferential reporting of Rely users among cases from California, Oregon, and Washington may have occurred in mid-August 1981 because of publicity about a case of TSS in a Rely tampon user. When the 15 cases from this area were excluded from analysis, the association of Rely brand tampons with TSS was still present ($P = .0017$;

relative risk, 5.5). In addition, the proportion of Rely users among cases in our study reported to us before Aug 15, 1980 (66%), was identical to the proportion reported to us after this case was publicized.

Tampon absorbency as a risk factor was analyzed in a linear logistic regression model that included brand name and absorbency as the two variables. Absorbency was determined by labeled absorbency of the tampon, by absorbency of each product line according to an in vitro method using an artificial vagina (syngyna), and by absorbency according to the volume of defibrinated blood absorbed from a beaker. With Rely brand included in the statistical model, no significant influence of absorbency was found that could be separated from the risk associated with using Rely brand tampons. Table 3 shows that the relative risk of illness associated with absorbency was approximately 1.0 with Rely brand in the model, while the relative risk of illness for Rely users was between 3.6 and 8.8 with absorbency in the model.

No differences between cases and controls were found for the number of tampons used during the menstrual period, use of more than one tampon at a time, use of tampons during nonmenstrual days, or douching practices.

The data establishing an increased risk of TSS among users of Rely tampons were presented to the Food and Drug Administration and the manufacturer immediately after completion of the study. The manufacturer voluntarily withdrew Rely tampons from the market in September 1980.

Follow-up Survey

Sixty-eight percent of cases and 43% of control subjects who were sent the follow-up questionnaire returned it. Four (11.8%) of 34 cases were using tampons at the time of follow-up, compared with 50 (100%) of 50 cases using tampons at the time of illness ($P < .0001$, Fisher's exact test, one tailed). Forty-five (70.3%) of 64 control subjects were using tampons during the follow-up, compared with 125 (83%) of 150 control subjects during the summer of 1980 ($P = .026$, Fisher's exact test, one tailed). None

		Controls		
		2 of 2	1 of 2	
Cases Using Tampons	Yes	6	2	Triplets
	No	0	0	
		3 of 3	2 of 3	
Cases Using Tampons	Yes	17	17	Quadruplets
	No	0	0	
		4 of 4	3 of 4	
Cases Using Tampons	Yes	2	6	Quintuplets
	No	0	0	

Fig 2.—Tampon use for cases and controls with onset of illness in July and August 1980. Each box contains number of case-control triplets, quadruplets, and quintuplets distributed according to use or nonuse of tampons by cases and each of her two to four matched controls. $\chi^2(1 df) = 6.87$; $P < .01$ (Mantel-Haenszel); relative risk equals infinity.

Fig 3.—Exclusive use of Rely brand tampons by cases and controls, including only those case- and control subjects who used tampons. One quintuplet is not shown for cases who used Rely and her four controls, one of whom used Rely. Z value = 4.08; $P < .0001$; relative risk, 7.7 (99% confidence interval, 2.1 to 27.8).

		Controls Using Rely				
		1 of 1	0 of 1			
Cases Using Rely	Yes	0	4			Pairs
	No	0	2			
		2 of 2	1 of 2	0 of 2		
Cases Using Rely	Yes	3	3	7		Triplets
	No	0	3	4		
		3 of 3	2 of 3	1 of 3	0 of 3	
Cases Using Rely	Yes	1	1	5	4	Quadruplets
	No	0	1	1	1	

Brand	Cases, % (n=42)	Controls, % (n=113)
Rely	71	26
Playtex	19	26
Tampax	5	26
Kotex	2.5	11
OB	2.5	11

Brand	Relative Risk	95% CI
Rely	7.7	2.1-27.9
Playtex	0.7	0.2-2.7
Tampax	0.1	0.02-1.0
Kotex	0.2	0.01-2.8
OB	0.3	0.02-4.4

*Exclusive users of a single brand of tampon. TSS indicates toxic shock syndrome; CI, confidence interval.

of the case respondents had used tampons continuously during their recent period, while 44% of the control respondents who had used tampons used them continuously.

Analysis of questionnaire data for other risk factors associated with TSS was unrewarding; no association between TSS and hygienic or sexual practices was found. In addition, no association with socioeconomic status, occupation, previous medical history (including previous streptococcal or staphylococcal infections), or contact with medical care practitioners was seen.

COMMENT

In this study, we were able to confirm the epidemiologic association of tampon use with the development of TSS in menstruating women. In addition, our data suggested that women using Rely brand tampons were at greater risk of acquiring TSS than users of other tampon brands. Other investigators have confirmed the increased risk of TSS in users of Rely brand tampons.^{9,10} However, the epidemiologic association of tampons in general and Rely specifically with TSS remains unexplained. It is clear that the use of tampons alone does not cause TSS, as cases of TSS have been described in women using other menstrual devices, in nonmenstruating women, and in men. It has also become evident that TSS is strongly

	Relative Risk	95% CI
Labeled absorbency	0.99	0.4-2.5
Rely	3.6	1.7-23.6
CDC-determined absorbency	1.03	0.3-3.9
Rely	4.8	1.2-20.2
Syngyna-determined absorbency	1.3	0.7-2.5
Rely	8.8	1.7-45.9

*For exclusive users of a single brand. Absorbency and Rely brand are independent variables in a logistic regression model. TSS indicates toxic shock syndrome; CI, confidence interval; and CDC, Centers for Disease Control.

associated with colonization or infection of patients with strains of *S aureus* capable of producing two newly described staphylococcal exotoxins—pyrogenic exotoxin C and enterotoxin F.^{4,5}

Little evidence has been developed to date to support a number of possible hypotheses explaining the association of tampons and *S aureus* with TSS. These hypotheses include intrinsic contamination of Rely or other tampon brands with *S aureus* during manufacture, the transmission of toxin-producing capabilities from other bacterial species, and enhancement of growth or toxin production by newer tampon products.

Although there is a temporal relationship between the introduction of new tampon products in the mid-1970s and increasing numbers of TSS cases reported dating from this period, our study did not support the hypothesis, advanced by others,⁹ that regardless of brand name, high-absorbency tampons are associated with an increased risk of development of TSS.

Because the epidemiologic association of tampons in general, and Rely tampons specifically, with TSS has not led to any unifying hypothesis about the pathogenesis of TSS in menstruating women, questions have been raised about the validity of these associations. Although the results of case-control studies can be affected by several biases, our study was designed to minimize biases in case and control selection, recall of distant events, and method of interview. We did not select cases from a "pool" of reports; all surviving cases with onset in July or August 1982, meeting the case definition, and reported before the start of the study were included. Acquaintance controls would be matched for socioeconomic status, as well as for exposure to the same

advertising and other sales promotion activities related to tampon or sanitary napkin use. The controls, therefore, may well have been overmatched for tampon brand use. Although we thus ran the risk of not being able to show an association that actually existed with tampons or a tampon brand, the demonstrable differences in tampon and tampon brand use between cases and controls are all the more striking because of this potential overmatching.

Our study was not blinded; interviewers knew both the hypotheses to be tested and the case-control status of participants. However, the questionnaire and the interview preamble were structured to eliminate the possibility of open-ended discussion of the use of menstrual devices. In addition, to confirm accurate recall, cases and controls using tampons were asked to obtain and read the label of the tampon box to the interviewer over the telephone.

Of particular concern is the possibility that widespread publicity about TSS in the lay press may have led to biased reporting of tampon-associated cases and Rely-associated cases to the CDC. The initial studies establishing the association of tampon use with TSS in menstruating women were completed and published before national public awareness of this association.^{2,3} The present study was performed during a period of heightened interest in and knowledge of the association of tampon use with TSS. The fact that no case reported to us during July and August 1980 had used a menstrual device other than tampons may have reflected the increased public awareness of the previously established link between tampons and TSS. The higher odds ratio for tampon use in the second CDC study would support this possibility. However, our results establishing the

increased risk associated with Rely brand tampons were obtained at a time when no assumptions about the specific risk of using Rely brand tampons were generally publicized. A case of TSS did occur in a Rely user living in northern California and received local television and newspaper coverage in mid-August 1980, before the initiation of our study. However, exclusion of cases from this area and exclusion of cases reported after Aug 15, 1980, did not affect the

results of the study, suggesting that preferential reporting of Rely users did not account for the strong association of TSS with Rely use found in our study.

Since removal of Rely tampons from the market, a decrease in the number of menstrually associated TSS cases reported to the CDC has been noted,¹¹ despite increased awareness of the syndrome by health care providers and the public. Although other factors may play a role in this

decrease, including the overall decrease in tampon use as seen in control women in our follow-up study, a decrease in reported cases of TSS is compatible with the major conclusion of our study that TSS was more likely to develop in women using Rely brand tampons than in women using other tampon brands.

Many physicians across the country reported cases of TSS to us. Jane Mayton prepared the manuscript.

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