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Research Paper

Association of characteristics of tampon use with menstrual toxic shock syndrome in France

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SUMMARY

Background: Menstrual tampons are widely used in western countries. Indirect evidence suggests that tampon misuse could be associated with an increased risk of menstrual toxic shock syndrome (MTSS). The aim of this study was to determine what characteristics of tampon use are associated with increased risk of menstrual toxic shock syndrome (MTSS).

Methods: A nationwide, case-control study in France, was conducted with women that use tampons with MTSS diagnoses according to the CDC diagnostic criteria (n = 55, from January 2011, to December 2017) and a control group of women with no MTSS history (n = 126, from February to December 2017). Information regarding tampon use during a 6-month period was collected. Associations between tampon use and MTSS were assessed using logistic regression models stratified by residential area.

Findings: Compared to controls, women diagnosed with MTSS more frequently reported maximum tampon wear of >6 h (62% vs. 41%; P = 0.02), overnight tampon use (77% vs. 54%; P = 0.006), and neither read nor followed tampon instructions in case of reading (65% vs. 42%; P = 0.006). In univariate analysis, MTSS risk was two-fold higher with tampon use for >6 consecutive hours (odds ratio, 2.3 [95% CI, 1.2–4.5]), and three-fold higher with tampon use during sleep for >8 h (odds ratio, 3.2 [95% CI, 1.4–7.7]). In multivariate logistic regression analysis, only maximum tampon use for >6 h (odds ratio, 2.03 [95% CI, 1.04–3.98]), and neither read nor followed the tampon instructions in case of reading (odds ratio, 2.25 [95% CI, 1.15–4.39]) were independently associated with MTSS.

Interpretation: Our study suggests that the risk of MTSS was associated with using tampons for more than 6 h, overnight tampon use during sleep, and neither read nor followed tampon insertion instructions in case of reading.

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1. Introduction

Staphylococcal toxic shock syndrome (TSS) is an acute onset illness caused by *Staphylococcus aureus* strains that can produce superantigenic exotoxins, such as toxic shock syndrome toxin-1 (TSST-1) [1,2]. TSS is characterized by non-specific symptoms, such as fever, cutaneous signs (rash followed by desquamation), digestive disorders, myalgia, and hypotension [3]. While TSS is often initially self-limited, it is a potentially serious disease that can rapidly lead to multiple-organ failure and death [3,4]. TSS treatment requires early ICU involvement for fluid resuscitation and possible vasopressors, and intravenous antibiotics with anti-staphylococcal agents and with anti-toxinic antibiotic such as clindamycin [4].

TSS is subdivided into two major categories: non-menstrual TSS that occurs during the course of suppurative staphylococcal infections [5], and menstrual toxic shock syndrome (MTSS) that occurs in young women with vaginal colonization of TSST-1-producing *S. aureus* and who use tampons [6,7] or other intra-vaginal devices [8,9].

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Research in context

Evidence before this study

Menstrual toxic shock syndrome (MTSS) is an uncommon acute illness that occurs in young women with vaginal colonization of TSST-1-producing *Staphylococcus aureus* and use tampons or other intra-vaginal devices. We searched literature databases with the medical subject headings «toxic shock syndrome» AND «menstruation» AND «Tampon» (Web of Knowledge, MEDLINE, PubMed) up to December 31, 2016, with no language restrictions. From our analysis there is evidence that women who use tampons or other intra-vaginal devices are at risk of menstrual toxic shock syndrome (MTSS), with an incidence around 1–3 cases per 100,000 menstruating women. In addition to tampon use, at least to two other conditions are considered necessary for MTSS development: vaginal colonization by a TSST-1-producing *S. aureus* strain and the absence of protective antibodies against TSST-1. These conditions are much more frequent than the incidence of MTSS, suggesting that only a minor subset of these predisposed women will actually develop MTSS and that other factors are involved in disease occurrence, such as how tampons are used. This question was mainly investigated during the outbreak in the 1980s, resulting in the removal of tampons made of carboxymethylcellulose fibers from the market and the implementation of mandatory labelling.

Added value of this study

This nationwide, case-control study conducted in France with women that developed MTSS and a control group supports existing evidence that differences in tampon use still contribute to the elevated risk of MTSS. Our findings suggest an increased risk of MTSS in women who use a tampon for over 6 consecutive hours, use a tampon when planning to sleep, do not perceive risk of MTSS when using tampon, and neither read nor followed the instructions provided in tampon pack in case of reading. Our study also identified a lack of women's education about tampon use in French populations.

Implications of all the available evidence

Our study suggests that for currently marketed tampons made of cotton of cellulose fibers, there is a lower risk of MTSS for women that read and follow the instructions provided in tampon pack. However, maximum wear-time per tampon should be 6 h, not 8 h as the FDA currently recommends. French women have a low level of knowledge about MTSS because initial education provided by family members and relatives was disconnected from the risk of MTSS. Public heath policies for MTSS prevention should be targeted to adolescents and involve more health professionals as sources of knowledge, because of their in-depth knowledge about MTSS.

MTSS received attention in the early 1980s, upon the description of cases and deaths among healthy women using tampons made of high-absorbency carboxymethylcellulose fibers [10,11]. Following the removal of these specific tampons from the market and their replacement with tampons made of cellulose or cotton fibers [12], the implementation of mandatory labelling [13], and improved patient education [6], the annual MTSS incidence in the United States (US) decreased from 10 cases to approximately 1–3 cases per 100,000 menstruating women [3,14]. The US Food and Drug Administration (FDA) recommended the inclusion of instructions that limit wear-time per tampon to no more than 8 h and advise against the overnight use of tampons [3,13]. There has been no active worldwide surveillance of this disease since 1986, making assessment of its incidence challenging [3,15–17]. A study conducted in the US suggested that TSS incidence increased by 18% from 2002 to 2003 [15]. The same trend has been reported in France since 2003 by the Centre National de Reference des Staphylocoques (CNRS) (http://cnr-staphylocoques.univ-lyon1.fr/). However, no studies have investigated this apparent rise of MTSS, its potential reasons, or determinants.

At least three conditions are considered necessary for MTSS development: vaginal colonization by a TSST-1-producing *S. aureus* strain [18–20], a vaginal environment conducive to TSST-1 production due to the use of intra-vaginal protection during menses [6–9], and the absence of neutralization antibodies against TSST-1 [6,7,21]. Since western populations exhibit a high prevalence (60–80%) of tampon exposure [22], MTSS might remain a significant public health issue. Among women who use tampons, 1–5% are vaginally colonized with TSST-1-producing *S. aureus*, and 10–20% of women have no protective antibodies against TSST-1 [18,23]. The low incidence of MTSS suggests that only a minor subset of these predisposed women will actually develop MTSS, and that other factors are involved in disease occurrence, such as how tampons are used, which was pointed out during the outbreak in the 1980s with tampons made of carboxymethylcellulose fibers [6,7,10]. However, there are limited published studies regarding the association between MTSS and the use of currently marketed tampons made of cotton or cellulose fibers, leaving many unanswered questions.

The aim of the present study was to characterize the use of tampons in women who developed MTSS. Our secondary objectives were to evaluate education regarding tampon use. The present results may offer practical guidance for the development of preventive public health strategies.

2. Methods

2.1. Study design and participants

To examine the relationship between tampon use and MTSS in women between 12–30 years of age, a nationwide, case-control study was performed with incident cases in metropolitan areas of France. The case population included women with a clinical diagnosis of MTSS that was reported to the CNRS of Lyon between January 1, 2011 and December 31, 2017, and which included vaginal detection of TSST-1-producing *S. aureus* strain and clonal complex (CC) assignation by the CNRS [24]. All suspected cases were assessed according to the Centers for Disease Control and Prevention (CDC) diagnostic criteria [25]. Cases meeting all five clinical criteria were considered confirmed. Those lacking a single criterion were considered probable. Confirmed and probable cases involving tampons, and with symptom onset occurring within three days of the beginning or end of menses [5], were eligible for inclusion. Control participants comprised women with no past history of MTSS, of 12–30 years of age, and who used tampons as menstrual protection (Data collection and control of potential bias in the Supplement). They were enrolled between February 1, 2017 and December 31, 2017. Cases suspected of using only menstrual cups (one woman during the inclusion time) or controls suspected of using only pads or menstrual cups were excluded.

Applying our eligibility criteria, a total of 78 cases were identified from the CNRS database. During the same period, only two MTSS cases of women age >30 were notified to the laboratory; they were not included in our study. All eligible participants (and their mothers, if the patient was below 18 years old) were invited by mail or phone to participate in the study on tampon usage and MTSS. Of the 78 cases contacted, 55 agreed to participate, yielding a 70% positive response rate. Cases were retrospectively contacted in February 2017 and asked to fill the questionnaire according to the use and knowledge they had before they developed the MTSS. Healthy women nationwide were enrolled in the

control population by IFOP© (www.ifop.fr), a professional survey institute specializing in national surveys conducted in the general French population. Using the non-probabilistic "quota" method 126 participants of 12–30 years of age were contacted and completed the questionnaire on tampon usage and MTSS (Data collection and control of potential bias in the Supplement). The case-control study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

This study was reviewed and accepted by the ethics committee (Comité de Protection des Personnes Sud Est IV, Centre Leon Berard, Lyon, France, N° L16-176). Written consent was obtained from all participants, or from the parents/guardians of participants under 18 years of age.

2.2. Procedures

For this study, the main exposure was tampon use. Upon finding no standard definition in the literature how tampons should be used, we relied on the usage precautions cited in the guidance document and the recommendations of the FDA [14]. The variable "tampon use" was evaluated using the following criteria: use of tampon outside of menses, forgetting to remove a tampon before inserting a new one, using a tampon with an absorption level not matching the menstruation flow, and/or using a tampon for over 8 h. Additionally it was decided to test the impact of wearing a tampon for over 6 h, which is frequently cited by practitioners [27–29].

Data were retrospectively collected using a specially-designed, self-administered, anonymous questionnaire (Questionnaire in the Supplement), which was similar for both cases and controls. It included questions regarding the terms of tampon use during the 6 months prior to MTSS for cases, and during the 6 months before the interview for controls. The questionnaire also included questions regarding how the women had learned how to use tampons; questions to evaluate their level of knowledge about MTSS; and questions about demographic data, such as age and residential area.

2.3. Statistical analysis

Statistical analysis was performed using the language *R* version 3.5.2, available at https://cran.r-project.org/. Knowing that 55 cases could be included in the study and assuming that the prevalence of tampon use was 60% in general population, it was calculated that at least 125 controls had to be recruited to identify a significant effect with 80% power at the 5% level, and to detect an odds ratio (OR) of at least 2.8 (pwr *R* package).

The questionnaire responses comprised quantitative and categorical data. There were no missing data for the main exposure of interest (maximum of tampon wearing time) and no imputation were conducted for missing data. The results were reported as median and interquartile (IQR) for non-normally distributed quantitative variables, and as frequencies and relative frequencies for categorical variables. The case and control populations were compared using the non-parametric Wilcoxon test for quantitative variables, and the Fisher's exact test for categorical variables. Some quantitative variables were categorized and some qualitative variables were constructed by pooling different items belonging to the same question as detailed in the Supplement.

The residential area was divided into four geographic areas: northwest, northeast, southwest, and southeast. ORs and their 95% confidence interval were estimated using univariate logistic regressions stratified by geographic area with case-control status as the dependent variable (Y), and questionnaire variables related to tampon misuse, MTSS knowledge or education as independent variables (X). Multivariate analysis with forward selection was performed including variables that were significant at the 10% level in univariate analysis. At each step the full model was adjusted and simplified by removing non-significant coefficients at 5% beginning with interaction coefficients. The final model was reported. The association between education variables and tampon use variables were assessed using Fisher exact test in the control population. Logistic regressions were performed using the Epi *R* package (function clogistic).

2.4. Role of funding

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

Base on the CDC definition, 30 patients (55%) met the definition for confirmed TSS and 25 (45%) for probable TSS. The demographic, the clinical and microbial characteristics, and the outcome of the 55 cases are summarized in Table 1. Cases age ranged from 12 to 30 years of age, with a median age of 17.9 years (IQR, 16.0–21.7 years). None of the patients had co-morbidities. Medical care in an intensive care unit was required for 47 patients (85%). No patient died from MTSS. TSST-1 producing *S. aureus* isolates recovered from tampon or vaginal specimens were methicillin susceptible and belonged predominantly to the same clonal complex CC30. Among the 55 cases, 14 (24%) reported using a tampon for over 8 h, and 34 (62%) for over 6 h during the day (Table 2). The median duration of maximum tampon wear was 8 h (IQR, 5–8.5 h). Tampon usage when planning to sleep > 8 h was reported by 40/52 cases (77%). Regarding absorbency choice, 23/53 cases (43%) indicated that they did not select a tampon with an absorption level corresponding to the intensity of their menstruation. Anticipatory use outside of menses was reported by 14 cases (24%), and 4 cases (7%) reported having forgotten to remove a tampon

Table 1
Clinical and microbial characteristics of 55 French patients with menstrual toxic shock syndrome (2011–2017).

Characteristics	MTSS, n = 55 (%)
Age in years, median ± IQR	17.9 (16.0–21.7)
Comorbidity	0 (0)
Hospitalization in an intensive care unit	47 (85)
CDC diagnostic criteria*	
Confirmed cases	30 (55)
Probable cases	25 (45)
Fever (≥39°C)	55 (100)
Hypotension or	55 (100)
Rash§	52/54 (96)
Desquamation§	37/48 (77)
≥3/7 Organ involvement§	45/55 (100)
Digestive§	45/55 (82)
Muscular§	33/49 (67)
Mucosal§	38/52 (73)
Renal§	30/54 (55)
Hepatic§	30/52 (58)
Hematologic§	17/52 (33)
Neurologic§	7/50 (14)
Mortality	0 (0)
Characteristics of *S. aureus* vaginal isolate, n (%)	
CC6, *tst*$^+$, *mecA*$^-$	1 (2)
CC8, *tst*$^+$, *mecA*$^-$	1 (2)
CC30, *tst*$^+$, *mecA*$^-$	52 (94)
CC45, *tst*$^+$, *mecA*$^-$	1 (2)

CC denotes clonal complex, *tst*$^+$ presence of *tst* gene coding for TSST-1, *mecA*$^-$ absence of mecA gene, IQR interquartile range, and MTSS menstrual toxic shock syndrome.

* Definition of probable or confirmed TSS cases was base on CDC definition [26] with 5 criteria: fever, hypotension rash, late desquamation, and minimum of 3/7 organ involvements. TSS cases were confirmed when 5/5 criteria were present, and probable it was only 4/5 criteria.

§ n/total (%).

Table 2
Comparison of between case and control populations.

Characteristics	Cases*n* = 55 (%)	Controls*n* = 126 (%)	P[#]	Odds ratio[†] (95%CI)
Geographic area[*]				
Northwest	19/55 (34)	43/126 (34)	0.8	
Northeast	7/55 (13)	12/126 (9)		
Southwest	7/55 (13)	21/126 (17)		
Southeast	22/55 (40)	50/126 (40)		
Age in years, median ± IQR	17.9 (16.0–21.7)	18.0 (16.0–24.8)	0.3	
Tampon misuse practices				
Maximum hours of tampon-wearing time, median ± IQR[§]	8 (5–8.5)	6 (4–8)	<0.05	
At least once >6 h[*]	34/55 (62)	52/126 (41)	0.01	2.33 (1.21–4.47)
At least once >8 h[*]	14/55 (24)	20/126 (16)	0.15	1.77 (0.81–3.84)
Tampon use when planning to sleep > 8 h[*,a]	40/52 (77)	65/120 (54)	0.006	3.22 (1.37–7.69)
Never match tampon absorbency to the menstruation flow[*]	23/53 (43)	41/126 (33)	0.18	1.56 (0.81–2.99)
Tampon use due to anticipation outside of menses[*]	14/55 (24)	38/126 (30)	0.59	0.81 (0.40–1.66)
Forgot to remove a tampon before inserting a new one[*]	4/55 (7.3)	12/126 (9.5)	0.78	0.76 (0.24–2.48)
MTSS knowledge				
Aware[*]	19/55 (35)	48/126 (38)	0.73	1.14 (0.59–2.22)
Perceived risk linked to tampon[*]	13/54 (24)	52/126 (41)	0.03	2.14 (1.05–4.36)
Know what to do if warning signs[*]	26/41 (63)	29/39 (74)	0.34	0.68 (0.25–1.85)
Initial education before first tampon use and skill acquisition				
Had initial education[*]	21/55 (38)	56/126 (44)	0.51	0.75 (0.39–1.43)
Among those educated for tampon use				
How to use tampons[*]	21/21 (100)	45/56 (80)	0.03	-
Precaution regarding tampon use[*]	11/21 (52.4)	36/56 (64.3)	0.43	0.51 (0.17–2.51)
Warning signs of MTSS[*]	1/21 (4.8)	4/56 (7.1)	1	0.61 (0.07–5.59)
What to do if MTSS suspected[*]	1/21 (4.8)	2/56 (3.6)	1	1.31 (0.12–4.81)
Source of education				
Members of the family or friend[*]	40/55 (73)	77/126 (61)	0.18	1.68 (0.84–3.34)
Health practitioner[*]	7/55 (13)	13/126 (10)	0.62	1.23 (0.46–3.27)
Media (internet, book, newspaper)[*]	16/55 (29)	35/126 (28)	0.86	1.06 (0.53–2.13)
Read the instructions provided in tampon pack[*]	32/55 (58)	98/126 (78)	0.01	0.41 (0.21–0.81)
Read and followed the instructions[*]	19/55 (35)	73/126 (58)	0.006	0.39 (0.21–0.76)

[*] n/total (%).
[§] IQR denotes interquartile range, MTSS menstrual toxic shock syndrome, and 95%CI 95% confidence interval.
[#] P value, Wilcoxon rank sum test for quantitative variables and Fisher's exact test for qualitative variables.
[†] The ORs and their 95% CI were estimated using univariate logistic regression model stratified for geographic area for each exposure variable in turn.

before inserting a new one. Concerning the level of knowledge about MTSS, 19 cases (35%) had heard about MTSS, and 13/54 (24%) knew that improper use of tampons could cause MTSS. Only 21 (38%) had received initial MTSS education before their first tampon use. From this initial education, only 1/21 (5%) learned the early warning signs of MTSS, and 1/21 (5%) learned what to do if these signs occurred. Mothers and other relatives were cited as the primary source of information by 40 cases (73%), followed by self-learning using media (internet, books, journals…) for 16 cases (29%). Only 7 cases (13%) reported having been educated by a health practitioner. Thirty-two cases (58%) had read the instruction form included in the tampon pack, and only 19 (35%) stated that they read and followed those instructions. To avoid information bias, the impact of the time-lag between exposure and interview on the answers was examined. Only 3/19 variables were associated with the time lag: "Forgot to remove a tampon before inserting a new one"($p = 0.04$), "Read the instruction provided in tampon pack" (0.02) and "Had initial education" (0.015).

The 126 controls ranged from 13 to 30 years of age, with a median age of 18.0 years (IQR, 16.0–24.8 years) (Table 2). Twenty (26%) reported using a tampon for over 8 h, and 52 (41%) for over 6 h during the day. The median duration of maximum tampon wear was 6 h (IQR, 4–8 h). Tampon usage when planning to sleep >8 h was reported by 65/120 controls (54%). Regarding absorbency choice, 41 controls (33%) indicated that they did not select a tampon with an absorption level corresponding to the intensity of their menstruation. Anticipatory use outside of menses was reported by 38 controls (30%), and 12 (10%) reported having forgotten to remove a tampon before inserting a new one. Concerning the level of knowledge about MTSS, 48 controls (38%) had heard about MTSS, and 52 (41%) knew that improper use of tampons could cause MTSS. Only 56 (44%) had received initial education before their first tampon use. From this initial education, only 4/56 (7%) learned the early warning signs of MTSS, and 2/56 (4%) learned what to do if these signs occurred. Mothers and other relatives were cited as the primary source of information by 77 controls (61%), followed by self-learning using media (internet, books, journals…) for 35 controls (29%). Only 13 controls (10%) reported having been educated by a health practitioner. Ninety-eight controls (78%) had read the instruction form included in the tampon pack, and 73 (58%) stated that they read and followed those instructions.

Comparison between cases and controls revealed differences in median of maximum tampon-wearing time (8, [IQR, 5–8.5] h vs. 6 [IQR: 4–8] h; $P < 0.05$) (Figure S1), in the percentage having a maximum tampon-wearing time of >6 h (62% vs. 41%; $P = 0.01$), and in the percentage using tampons during sleep >8 h (77% vs. 54%; $P = 0.006$). Notably, cases were less likely to know the MTSS risk of tampon use (24% vs. 41%; $P = 0.03$), to have read the tampon instructions (58% vs. 78%; $P = 0.01$), and to read and follow the tampon instructions (35% vs. 58%; $P = 0.006$). No difference in educational level or socioeconomic status was observed between the two groups.

The final model obtained from multivariate analysis contained two independent variables without interaction: "maximum wearing time of >6 h" (OR, 2.03 [95% CI, 1.04–3.98]; $P = 0.04$), and "neither read nor followed the tampon instructions in case of reading" (OR, 2.25 [95% CI, 1.15–4.39]; $P = 0.02$). Results' summary of the complete multivariate regression analyses and details on the variable definition are reported Table S2 in supplement.

Education regarding tampon use was strongly related to tampon misuse; therefore, an in-depth analysis of tampon education was performed in the control population (Table 3). With regards to the usage precautions cited in the guidance document and the FDA recommendations, women educated by their mothers and other relatives were

Table 3
Tampon Misuse according to source of Tampon use education in the control population.

Education	Tampon misuse*	Control population n = 126 (%)		$P^{\#}$
Family member or friend as educator		Yes (n = 77)	No (n = 49)	
	Use tampon if planning to sleep > 8 h[§]	34/73 (47)	31/47 (66)	0.04
Read the instructions		Yes (n = 73)	No (n = 25)	
	Tampon wearing maximum time > 6 h[§]	25/73 (34)	14/25 (56)	0.06
	Tampon wearing maximum time > 8 h[§]	7/73 (9.6)	8/25 (32)	0.02
	Use tampon if planning to sleep > 8 h[§]	32/69 (47)	18/24 (75)	0.02
Read and followed the instructions		Yes (n = 73)	No (n = 53)	
	Tampon wearing maximum time > 6 h[§]	25/73 (34)	27/53 (51)	0.07
	Tampon wearing maximum time > 8 h[§]	7/73 (9.6)	13/53 (25)	0.03
	Use tampon if planning to sleep > 8 h[§]	32/69 (46)	33/51 (65)	0.06
	Tampon use due to anticipation outside of menses[§]	16/73 (22)	22/53 (42)	0.03

* Only variables with $P \leq 0.1$ are shown.
§ n/total (%).
\# P value: Fisher's exact test.

only less inclined to use a tampon when they were planning to sleep (47% vs. 66%; P = 0.04). Women who read the instructions from a tampon package reported less frequent tampon use for >8 h (9.6% versus 32%; P = 0.02) and during the night (47% vs. 75%; P = 0.02). Women who indicated that they read and followed the tampon instructions reported a lower rate of tampon use for >8 h (9.6% vs. 25%; P = 0.03) and of tampon use due to anticipation outside of menses (22% vs. 42%; P = 0.03). In our control population, education from a health practitioner had no impact on tampon proper use, nor did media access (e.g., websites, books, and journals). None of the reported education was associated with a better understanding of the link between tampon use and MTSS (data non shown).

4. Discussion

The present study screened for a potential relationship between tampon use and MTSS. Our results show that MTSS is still a severe disease, and suggest that increased MTSS risk was associated with using a tampon for over 6 consecutive hours (OR = 2.33), overnight tampon use (OR = 3.22), and lack of education about tampon use. These findings suggest that MTSS risk may increase starting at tampon use $\geq$ 6 h, rather than from 8 h, and that women could be advised to wear a tampon for a maximum of $\leq$ 6 consecutive hours rather than the currently recommended maximum of $\leq$ 8 h [13]. Although prior studies have investigated the impact of tampon wearing duration on MTSS occurrence, this topic has not been addressed recently, with the currently marketed tampon varieties. The conclusions of prior studies for maximum hours of tampon wearing time were mainly based on the number of tampons to use per day in patients and in vitro experiments [7,29]. They were in close agreement with our present findings [7,29]. Our results specify (in number of hours) when the risk increase begins and additionally support the current recommendation to use sanitary napkins or menstrual panties rather than tampons during the night, especially for women who sleep for more than 6 h [7,13,29].

Compliance of women with FDA recommendations [13] and labelling instructions for tampon use are essential for MTSS prevention. Yet, our present results indicated that while tampon wearing time recommendations are usually followed by women, in keeping with the findings of previous studies [30–32], a large majority of respondents did not follow one or more of the labelling recommendations. Our study points out a persistent level of tampon misuse practices, and the need to promote safer tampon use. The surveyed also revealed that women had a low level of knowledge about MTSS. To date, few studies have investigated women's knowledge of MTSS, and many of the available studies were performed in the 1980s [33,34]. In 1985, a survey reported a lack of knowledge regarding MTSS among adolescents [33]. Our present findings suggest that this issue persists today, and may be even more prevalent than previously reported.

Safer tampon use and improved knowledge of MTSS are closely linked to learning modalities [28,31,33–35]. Our present data suggest that education on tampon use is still deficient in France. Most notably, it was observed that the majority of women did not receive initial education about tampons prior to use and this education was frequently disconnected to the risk of MTSS. It is important that adequate menstrual hygiene habits be formed at the beginning of adolescence [35,36], as such habits will influence adult behaviors [37–41]. To obtain knowledge about tampon use, adolescents frequently discussed the topic with their mothers or self-trained themselves by reading tampon labels, as previously described [34,36,39-42]. However, the high level of misuse practices suggests that these learning modalities are likely insufficient to teach women about tampon use and MTSS. It was discovered that health professionals were minimally utilized as sources of knowledge about tampon use, despite their in-depth knowledge about MTSS [34,43] and greater ability to influence behaviours by providing adequate information [28,34–36]. Overall, our study results confirmed findings from earlier studies and the absence of progress [28,34–36]. Education about tampon use still needs to be improved.

The main strength of this nationwide case-control study is that is exploring a question that has been scarcely investigated: which tampon use practices have an impact on MTSS occurrence? This topic is growing concern due to the apparent rise of MTSS cases reported in US, France and elsewhere [15]. In this context, our results highlight important avenues for improving MTSS prevention.

This case-control study has several potential limitations. The invitation to participate in the study on tampon usage and MTSS and the questionnaire may have influenced women's answers on tampon use and MTSS. There was no stratification by age for the control inclusion. The absence of medical history of potential MTSS for the control population was established by an interview only based on the absence of hospitalization for fever of shock during tampon use. However the disease is so uncommon that it was very unlikely to include women with history of MTSS as control. Only women vaginally colonized by TSST-1 producing *S. aureus* and with no protective antibodies against TSST-1 are really at risk of MTSS. It was unfortunately not possible to include these criteria for the selection of controls. Time of inclusion between control and case differs. Cases were retrospectively contacted in February 2017 while they developed their MTSS between January 2011 to December 2017. Cases were asked to fill the questionnaire according to the use and knowledge they had before they developed the MTSS. The time lag between the interview and MTSS onset could be greater than the 6 months used for control, and may have introduced recall bias for cases. However, except for "Forgot to remove a tampon before inserting a new one" and "Read the

instruction provided in tampon pack", no significant association between time-lag and variables were observed in cases, suggesting that length of time lag had little effect on the quality of their reporting and the analysis. Additionally, no information about tampon absorbency was collected.

Our findings suggest an increase risk of MTSS in women using a tampon for a duration starting from over 6 consecutive hours, overnight tampon use, and with lack of education about tampon use. There remains a need for further epidemiological research to confirm ours results and to more precisely identify MTSS facilitators and to fine-tune the MTSS prevention measures that will best improve women's health.

Contributors

AB, AT, PW and GL led the concept and design of the study. AB, AT, C-AG and GL did the data acquisition. AB, M-PG, TB JB, PW and GL did the statistical analysis. M-PG, TB, JB, C-AG and GL contributed to the drafting of the manuscript. All authors contributed to data interpretation and to critical revision of the manuscript.

Declaration of Competing Interest

Thomas Benet was employed by bioMérieux from January 2018 to October 2019, working in a topic outside of the submitted work. Claude-Alexandre Gustave reports grants from LABEX ECOFECT (ANR-11-LABX-0048) of Université de Lyon within the programme "Investissements d'Avenir" (ANR-11-IDEX-0007) operated by the French National Research Agency (ANR) during the conduct of the study. Philippe Vanhems reports grants and personal fees outsides the submitted work from Astellas, Biosciences, MSD and Pfizer.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100308.

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