HHS Public Access

Author manuscript

Obstet Gynecol. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Obstet Gynecol. 2016 February ; 127(2): 360–368. doi:10.1097/AOG.0000000000001239.

Vaginal and Rectal *Clostridium sordellii* and *Clostridium perfringens* Presence Among Women in the United States

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Abstract

OBJECTIVE—To characterize the presence of *Clostridium sordellii* and *Clostridium perfringens* in the vagina and rectum, identify correlates of presence, and describe strain diversity and presence of key toxins.

METHODS—We conducted an observational cohort study in which we screened a diverse cohort of reproductive-aged women in the United States up to three times using vaginal and rectal swabs analyzed by molecular and culture methods. We used multivariate regression models to explore predictors of presence. Strains were characterized by pulsed-field gel electrophoresis and tested for known virulence factors by polymerase chain reaction assays.

RESULTS—Of 4,152 participants enrolled between 2010 and 2013, 3.4% (95% confidence interval [CI] 2.9–4.0) were positive for *C sordellii* and 10.4% (95% CI 9.5–11.3) were positive for *C perfringens* at baseline. Among the 66% with follow-up data, 94.7% (95% CI 88.0–98.3) of those positive for *C sordellii* and 74.4% (95% CI 69.0–79.3) of those positive for *C perfringens* at baseline were negative at follow-up. At baseline, recent gynecologic surgery was associated with *C sordellii* presence, whereas a high body mass index was associated with *C perfringens* presence in adjusted models. Two of 238 *C sordellii* isolates contained the lethal toxin gene, and none contained the hemorrhagic toxin gene. Substantial strain diversity was observed in both species with few clusters and no dominant clones identified.

CONCLUSION—The relatively rare and transient nature of *C sordellii* and *C perfringens* presence in the vagina and rectum makes it inadvisable to use any screening or prophylactic approach to try to prevent clostridial infection.

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Presented at the National Abortion Federation's 38th Annual Meeting: Standing Tall, April 5–8, 2014, San Francisco, California; the Infectious Diseases Society for Obstetrics and Gynecology Annual Meeting, August 7–9, 2014, Stowe, Vermont; the North American Forum on Family Planning, October 12–13, 2014, Miami, Florida; and XXI FIGO (International Federation of Gynecology and Obstetrics) World Congress of Gynecology and Obstetrics, October 4–9, 2015, Vancouver, Canada.

Financial Disclosure

The authors did not report any potential conflicts of interest.

CLINICAL TRIAL REGISTRATION—ClinicalTrials.gov, www.clinicaltrials.gov, NCT01283828.

Clostridia are Gram-positive, spore-forming, anaerobic bacteria commonly found in soil and are relatively uncommon human pathogens.[1,2] Obstetric–gynecologic cases of *Clostridium sordellii* and *Clostridium perfringens* infections have resulted in a toxic shock-like syndrome[2–17] (Reis T, Chaves C, Soares A, Moreira M, Boaventura L, Ribeiro G. A *Clostridium sordellii* fatal toxic shock syndrome post-medical-abortion in Portugal, presented at the 21st European Congress of Clinical Microbiology and Infectious Diseases, May 7–10, 2011, Milan, Italy) with a high fatality rate.

Cases of fatal pelvic clostridial infections have followed events including miscarriage, full-term delivery, stillbirth, abortion, and cervical procedures. Eight of the deaths followed medical abortions with mifepristone and misoprostol, although no causal pathway has been identified.[18] A disproportionate number of cases occurred in the western United States.

The emergence of clostridial infections affected medical abortion services in the United States. In 2006, the Planned Parenthood Federation of America changed its Medical Standards and Guidelines to recommend buccal over vaginal administration of misoprostol and to require routine use of antibiotics after medical abortion,[19] most commonly 7 days of doxycycline or a single dose of azithromycin.[20] Many independent abortion providers chose to adopt the same measures.

Because clostridial pelvic infections are very rare, this observational cohort study explores clostridial presence. Primary objectives include: estimating the prevalence of *C sordellii* and *C perfringens* in the vagina, rectum, or both; exploring how presence changes over time; and identifying predictors of presence in exploratory analyses. Secondary objectives included describing strain diversity and identifying the presence of key toxins in the isolated strains.[21,22]

MATERIALS AND METHODS

Women aged 18–45 years not seeking or undergoing emergency or oncologic care were eligible to participate in the study. Twenty-five Metropolitan Statistical Areas were randomly selected weighted by population data from the 2007 U.S. Census. Counties were randomly selected within each Metropolitan Statistical Area (also weighted by population) within which suitable study sites were sought. Sites were selected to access a diverse patient population and included private obstetrics–gynecology practices, family planning clinics, abortion clinics, university hospital gynecology clinics, and research centers.

The study enrolled participants from November 2010 to April 2013, and participation involved up to three visits. Participants were screened for vaginal and rectal presence of *C sordellii* and *C perfringens* at the initial visit, were asked to return 2 weeks later for a second screening (which coincided with the follow-up visit for patients undergoing abortion), and participants who were positive at the second visit were asked to return for a third screening approximately 4 weeks after the second visit. After providing written informed consent, participants provided a detailed medical history, a study clinician took swab samples from

the vagina and from the rectum, measured vaginal pH, and prepared a Gram stain slide. All samples were obtained before any other procedures were performed. Additional diagnostics and care provided as part of the clinical visit were documented. Participants also completed a computer assisted self-interview survey to collect additional information on demographics, sexual and reproductive history, and other relevant behaviors. The survey was administered in either English or Spanish using online electronic data capture with DatStat Illume 4.11. At follow-up visits, vaginal and rectal swabs, vaginal pH, and Gram stains were collected. Participants underwent a physical examination and responded to a shortened version of the computer survey on behaviors and practices that occurred since the previous visit.

A central laboratory scored the Gram stains for bacterial vaginosis using Nugent Criteria[23] and screened swab specimens by culture and by polymerase chain reaction (PCR) for both *C perfringens* and *C sordellii*. During the pilot phase of the project when we tested the laboratory methods, PCR was better at detecting *C perfringens* and culture was better at detecting *C sordellii*; thus, a participant was considered "positive" if she had a positive result with either PCR or culture. Please refer to Appendix 2, available online at http://links.lww.com/AOG/A751, for specifics of culture and PCR methods. All isolates obtained through the study were sent to the Centers for Disease Control and Prevention (CDC) for confirmatory identification using the MALDI Biotyper and strain typing by pulsed-field gel electrophoresis and PCR. Conventional multiplex PCR assays were used to test for toxins. Please refer to Appendix 3, available online at http://links.lww.com/AOG/A751, for specific primers and probes used.

We selected a sample size of 4,000 to estimate the prevalence for both species of Clostridium at either anatomical site with a precision of ± 1% points at baseline. This sample size would also yield a substantial number of isolates for study by the CDC. Prevalence estimates were generated in SPSS 19.0, and bivariate analyses and multivariate regression models were conducted using Stata 12.1.

Because bacteria are transferred easily between the rectum and vagina and thus presence at either site could result in a pelvic infection, we combined vaginal and rectal presence for analyses of predictors as well as for changes in presence over time. Because the pathways of exposure and risk may differ for these two bacteria, we analyzed predictors for each bacterial species separately. We used generalized estimating equations with robust standard error estimation and exchangeable correlation structures to account for clustering of the observations by study site to explore predictors for the presence of *C sordellii* and *C perfringens* at baseline and at time two. We explored any variable that was statistically significant in the bivariate analyses for inclusion in the final adjusted models. We tested for correlations between covariates and selected which variables to include in our final adjusted model based on model fit and biological plausibility. We used a threshold of statistical significance of 0.001 based on a critical α value of 0.15 for these exploratory analyses with a Bonferroni adjustment for the 150 variables tested.

The study was approved by the New England institutional review board, the Colorado Multiple institutional review board, the University of Arizona institutional review board, and the University of Cincinnati institutional review board.

RESULTS

We found 26 suitable sites in 18 of the 25 randomly selected Metropolitan Statistical Areas. We enrolled and obtained baseline samples from 4,152 women; 2,755 women (66%) completed visit 2 procedures, and 255 of the 350 women positive at visit 2 (73%) completed visit 3 procedures (Fig. 1). The median days between visit 1 and visit 2 were 14 days (interquartile range 13–17). Participants were approximately evenly distributed among the four census regions, had an average age of 28.6 years, and 36% were patients who were undergoing abortion. In addition to seeking abortion services, other common reasons for presenting included study participation (26%), well-woman visits (21%), and gynecologic complaints (6%).

At baseline, 12.7% (95% confidence interval [CI] 11.7–13.7) of participants were positive for either species at either anatomical site; 10.4% (95% CI 9.5–11.3) were positive for *C perfringens* and 3.4% (95% CI 2.9–4.0) for *C sordellii*. Rectal presence was more common than vaginal presence for both species with 9.8% (95% CI 8.9–10.7) and 1.2% (95% CI 0.9–1.6) of samples screening positive for *C perfringens*, respectively, and 3.2% (95% CI 2.7–3.8) and 0.2% (95% CI 0.1–0.4) for *C sordellii*. Few participants had both species present (1%, 95% CI 0.7–1.3); and few had the same species in both anatomic sites (0.6%, 95% CI 0.4–0.9 for *C perfringens* and 0.05%, 95% CI 0.006–0.2 for *C sordellii*).

We tested more than 150 variables for associations with presence; Table 1 displays a small subset of these variables. In bivariate analysis, no statistically significant differences in presence of either species were found by age, race–ethnicity, household income, number of days since last menses, or vaginal pH. Predictors were rarely significant for both species.

In adjusted baseline models, having gynecologic surgery in the previous 3 months was significantly associated with *C sordellii* presence (Table 2; adjusted odds ratio [OR] 4.86, P5.001). For *C perfringens*, taking medication for a gastrointestinal disorder in the previous 3 months (adjusted OR 2.00, $P<.001$), ever having a surgical intervention related to abortion (surgical abortion or a surgical completion of a medical abortion; adjusted OR 1.40, $P=.001$), and body mass index (BMI, calculated as weight (kg)/[height (m)]^2) of 35 or greater (adjusted OR 1.83, $P<.001$) were significantly associated with presence. Medical abortion was not associated with presence of either species.

Of the participants who tested positive at baseline, 94.7% (95% CI 88.0–98.3) of patients positive for *C sordellii* and 74.4% (95% CI 69.0–79.3) of those positive for *C perfringens* were no longer positive by visit 2 (Fig. 1). Women positive for clostridia at visit 1 were more likely than negative women to be positive at visit 2. No related serious adverse events were reported.

Changes in *C sordellii* and *C perfringens* presence between visits 1 and 2 were not significantly different when comparing patients who had undergone abortion and nonabortion patients, medical abortion and surgical abortion patients, and those taking antibiotics compared with those who did not take any antibiotics.

In adjusted models for presence at visit 2, no variables were significant for *C sordellii*, although presence at baseline shows some relationship in the abortion participant-only model (Table 3). For *C perfringens*, lower education and presence at baseline show a strong association in the overall model, and BMI of 35 or greater and having two or more sexual partners since the previous visit shows some relationship. These results did not change when the analysis was restricted to women with 7–21 days between visits.

C perfringens isolates (n=212) and *C sordellii* isolates (n=238) were confirmed and characterized at the CDC. No *C sordellii* isolates were positive for hemorrhagic toxin and two (0.8%, 95% CI 0.1–3.0) were positive for lethal toxin. The two lethal toxin-positive isolates were from baseline rectal samples of surgical abortion participants from the West. Both participants tested negative for *C sordellii* at their second visit. Among the *C perfringens* isolates, 211 (99.5%, 95% CI 97.4–100) were positive for α toxin, and 175 (82.5%, 95% CI 76.8–87.4) were positive for θ toxin; none was positive for β or ε toxin.

Substantial strain diversity was observed in both *C sordellii* and *C perfringens* with few clusters and no dominant clones identified for either species. Twelve indistinguishable *C sordellii* and 18 indistinguishable *C perfringens* were recovered from more than one participant, nearly all of which were from different geographic locations. Significant strain diversity was found even among isolates recovered from the same participant. There were seven instances in which *C perfringens* was recovered from both rectal and vaginal samples at the same visit; in six cases, the strains were different. Of 15 instances when a participant had *C perfringens* isolated from the same anatomical site across visits (eg, positive vaginal sample at visits 1 and 2), 13 had different strains. For *C sordellii*, one of two participants with positive rectal and vaginal samples at the same visit carried a different strain, and eight of nine cases with isolates from the same site at different visits had different strains.

DISCUSSION

This study documents that vaginal and rectal presence of *C sordellii* is relatively rare and presence of *C perfringens* is more common in our sample of reproductive-aged U.S. women. In our regression models for *C sordellii*, only gynecologic surgery in the previous 3 months appeared significant at baseline (likely reflecting the opportunity for organisms to be introduced), and nothing was significant at visit 2. For *C perfringens*, BMI of 35 or greater was found to be significantly associated with presence of the bacteria at baseline and approached significance at visit 2. We also witnessed a trend of increasing ORs with increasing BMI, which may reflect reduced bacterial diversity[24,25] (and thus a more hospitable environment for clostridia) and a reduced ability for hygiene. Clostridial presence did not appear to be related to pregnancy status, antibiotic use, geographic region, or medical abortion.

From the women who screened positive and returned for a follow-up visit, we can infer that presence of *C sordellii* or *C perfringens* very rarely leads to adverse outcomes. Furthermore, it appears that the presence of these bacteria is transient with the majority of women screening positive changing status by the next study visit. As such, we prefer the term bacterial “presence” rather than “colonization” or “carriage.”

Because strains are usually only recovered and studied in cases of disease or death, the prevalence of strains containing virulence factors in a healthy population was not previously documented. For *C sordellii*, lethal toxin has been implicated in all the fatal cases in the literature, but only 2 of 238 strains in our sample contained that gene. Hemorrhagic toxin is also considered to play a large role in pathogenesis; however, no strains tested positive for this gene.

Although our sampling scheme was designed to enroll a diverse cohort of reproductive-aged women, the generalizability of this study's findings should be approached with caution. We used the computer assisted self-interview survey to encourage more honest reporting of sensitive behaviors,[26–28] but it is likely that there was still some underreporting, and this methodology may have been an obstacle for those participants who were less computer-literate.

Use of swab samples is vulnerable to sampling error, where clostridia may be present but the swab did not capture the bacteria. Swab samples were chosen over stool samples for logistic reasons, but it likely resulted in an underestimate of the presence of clostridia in the rectum. In addition, it is possible that the two species were present on the swabs but were not detected by culture and PCR methods either because of the difficulty of isolating the clostridia from the high number of other bacteria present or because clostridia were present in such low quantities that they were undetectable. The number of false-positives was minimal for PCR as a result of the specificity of the primers used. The CDC confirmed identification of all viable culture isolates using matrix-assisted laser desorption ionization time-of-flight mass spectrometry, and 95.1% of the original identifications were correct.

Because *C sordellii* and *C perfringens* presence was relatively rare, we may not have had sufficient power to detect predictors of presence, especially at the second visit when one third of our sample was lost to follow-up. Cohen's effect sizes comparing demographic characteristics of women who returned to those lost to follow-up at visit 2 were small (≤0.1), with the exception of region of residence which was medium (Cramer's V=0.2) (women in the South were more likely to be lost to follow-up). Because our study was not designed to bring back participants who were negative at visit 2 for a third visit, we cannot make accurate estimations of reappearance rates (those who went from positive to negative and back to positive).

This study suggests that the chances are exceedingly small that a woman would have *C sordellii* present in the vagina, that the lethal toxin gene would be present in that particular strain, and that the bacteria would remain long enough in the vagina and conditions would be suitable for the bacteria to flourish and produce toxins.

The rarity and transient nature of *C sordellii* and *C perfringens* presence make it inadvisable to use any screening or prophylactic approach to try to prevent clostridial infection. Presence is not predicted by any particular characteristic that could be used to target certain subgroups. Furthermore, based on these data, use of antibiotics at the time of medical abortion would likely not be effective at reducing the presence of clostridia or reducing clostridial infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by an unrestricted research grant from an anonymous donor, who had no involvement in the study design, data collection or analysis, or writing of the results.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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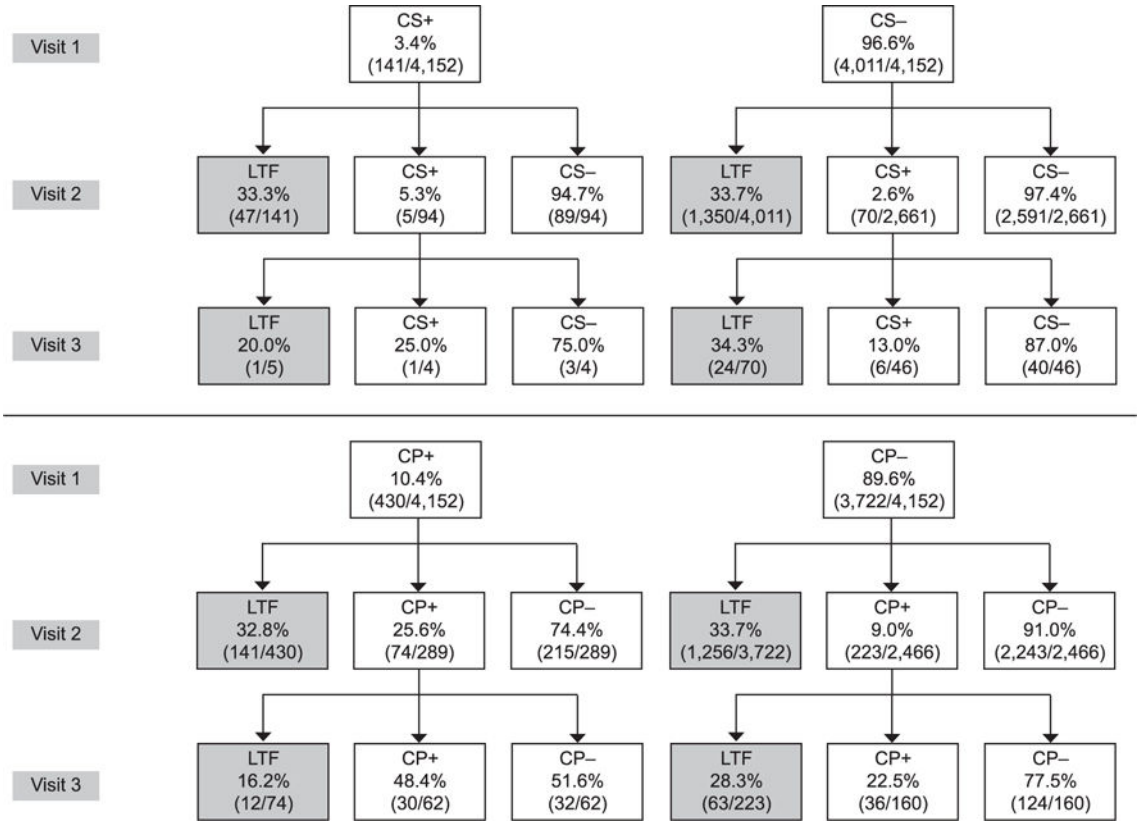

Fig. 1.

Presence of *Clostridium sordellii* (CS) and *Clostridium perfringens* (CP) across study visits. Denominators in boxes not marked LTF (lost to follow-up) indicate the number of participants for whom usable specimens for that visit were available.

Chong. Presence of Clostridia Bacteria in Women. Obstet Gynecol 2016.

Table 1

Presence of Any Site *Clostridium sordellii* and *Clostridium perfringens* at Baseline by Selected Participant Characteristics

		CS Presence				CP Presence			
Participant Characteristics	**Column %**	**n**	**N**	**Row%**	***P****	**n**	**N**	**Row%**	***P****
Total		141	4,152	3.4		430	4,152	10.4	
Age (y) (n=4,149)									
18–20	11.2	14	464	3.0	.139	54	464	11.6	.354
21–25	29.6	37	1,230	3.0		138	1,230	11.2	
26–30	24.2	48	1,005	4.8		109	1,005	10.8	
31–35	15.3	15	633	2.4		54	633	8.5	
36–40	10.4	13	430	3.0		39	430	9.1	
41–45	9.3	14	387	3.6		36	387	9.3	
Education (n=4,124)									
Less than high school	5.5	8	226	3.5	.563	35	226	15.5	.042
High school or high school equivalency certificate	21.8	26	900	2.9		103	900	11.4	
Some college or associates	41.5	54	1,712	3.2		176	1,712	10.3	
Bachelor’s degree	18.1	26	748	3.5		68	748	9.1	
Some graduate or graduate degree	13.0	24	538	4.5		47	538	8.7	
Race–ethnicity (n=4,121)									
White	46.7	60	1,925	3.1	.633	190	1,925	9.9	.659
Latina or Hispanic	11.6	20	478	4.2		48	478	10.0	
Black or African American	29.3	41	1,209	3.4		138	1,209	11.4	
Asian, Pacific Islander, or Hawaiian	3.1	6	129	4.7		11	129	8.5	
Other	9.3	11	380	2.9		41	380	10.8	
Region of current residence[†] (n=4,145)									
Northeastern United States	22.3	41	929	4.4	.255	100	929	10.8	.051
Southern United States	26.4	30	1,091	2.7		88	1,091	8.1	
Midwestern United States	24.3	37	1,009	3.7		116	1,009	11.5	
Western United States	26.8	33	1,110	3.0		125	1,110	11.3	
Outside the United States (including Puerto Rico)	0.1	0	6	0.0		0	6	0.0	
Currently live with partner or spouse (n=4,123)									

Participant Characteristics	Column %	CS Presence n	CS Presence N	CS Presence Row%	CS Presence *P**	CP Presence n	CP Presence N	CP Presence Row%	CP Presence *P**
Yes	39.0	57	1,607	3.5	.661	186	1,607	11.6	.036
No	61.0	83	2,516	3.3		239	2,516	9.5	
Currently pregnant (n=4,150)									
Yes	38.0	50	1,575	3.2	.596	182	1,575	11.6	.052
No	62.0	91	2,575	3.5		248	2,575	9.6	
BMI (kg/m^2) (n=4,128)									
Less than 18.5	2.8	2	116	1.7	.306	12	116	10.3	<.001
18.5–24.9	41.4	52	1,711	3.0		155	1,711	9.1	
25.0–29.9	25.2	32	1,039	3.1		91	1,039	8.8	
30.0–34.9	15.4	24	635	3.8		75	635	11.8	
Greater than 35.0	15.2	29	627	4.6		95	627	15.2	

CS, Clostridium sordellii; CP, Clostridium perfringens; BMI, body mass index.

*Fisher exact P.

†Northeastern United States (Connecticut, Delaware, Massachusetts, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont); Southern United States (Alabama, Arkansas, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia); Midwestern United States (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, North Dakota, Nebraska, Ohio, South Dakota, Wisconsin); Western United States (Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, New Mexico, Nevada, Oregon, Utah, Washington, Wyoming).

Table 2

Regression Models of Characteristics Associated With Baseline Presence of *Clostridium sordellii* and *Clostridium perfringens*

	Clostridium sordellii				Clostridium perfringens			
Participant Characteristics	**Crude OR**	***P****	**aOR (n=3,897)**	***P****	**Crude OR**	***P****	**aOR (n=3,855)**	***P****
Age	1.00	.970	1.00	.844	0.99	.107	0.98	.024
Race–ethnicity								
White (ref)	1.00		1.00		1.00			
Latina or Hispanic	1.37	.252	1.36	.291	1.01	.961		
Black or African American	1.12	.506	1.11	.489	1.18	.211		
Asian, Pacific Islander, or Hawaiian	1.48	.230	1.84	.042	0.87	.484		
Other	0.93	.894	0.80	.663	1.08	.754		
Education								
Less than high school (ref)	1.00				1.00			
High school or high school equivalency certificate	0.80	.574			0.71	.245		
Some college or associates	0.87	.727			0.63	.081		
Bachelor’s degree	0.97	.954			0.57	.159		
Some graduate or graduate degree	1.29	.528			0.54	.074		
BMI (kg/m^2)								
Less than 18.5	0.55	.587	0.63	.655	1.18	.653	1.00	.992
18.5–24.9 (ref)	1.00		1.00		1.00		1.00	
25.0–29.9	1.01	.962	1.04	.846	0.95	.774	0.95	.789
30.0–34.9	1.25	.340	1.35	.197	1.32	.013	1.31	.071
35 or greater	1.54	.105	1.74	.024	1.75	.001	1.83	<.001
Gynecologic surgery past 3 mo	3.75	.011	4.86	.001				
Ever been told had any STI	0.68	.005	0.75	.069				
Douche past 3 mo	0.61	.041	0.57	.017				
Never used a barrier method	1.66	.020	1.64	.031				
Currently live with partner or spouse					1.24	.041	1.27	.030
Heavy bleeding last menses					0.73	.014	0.69	.004
Ever anal sex with man					1.30	.006	1.34	.003
Ever surgical intervention for abortion					1.33	.004	1.40	.001

Participant Characteristics	Clostridium sordellii				Clostridium perfringens			
	Crude OR	*P**	aOR (n=3,897)	*P**	Crude OR	*P**	aOR (n=3,855)	*P**
Ever told had BV					0.78	.011	0.73	.004
Medication for GI disorder past 3 mo					1.69	.002	2.00	<.001
Ever thyroid disease					0.49	.017	0.45	.035
Asthma in past 3 mo					1.66	.001	1.51	.013
When took last antibiotic								
Currently taking (ref)	1.00		1.00		1.00		1.00	
4 wk or less	4.00	.199	4.11	.181	1.81	.291	1.61	.447
More than 4 wk ago	3.10	.278	2.75	.327	2.39	.069	2.23	.123
Never	6.54	.133	6.68	.125	3.70	.017	3.85	.010
Do not know	6.99	.081	6.76	.079	2.52	.012	2.78	.007

OR, odds ratio; aOR, adjusted odds ratio; ref, referent; BMI, body mass index; STI, sexually transmitted infection; BV, bacterial vaginosis; GI, gastrointestinal.

*Both crude and adjusted estimates are based on generalized estimating equation models to estimate robust standard errors after adjusting for clustering at the recruitment clinic or site using an exchangeable correlation structure. Adjusted models are fully adjusted for all of the variables listed with adjusted estimates in the respective column.

Table 3

Regression Models of Characteristics Associated With Visit 2 Presence of *Clostridium sordellii* and *Clostridium perfringens*

	Clostridium sordellii				Clostridium perfringens			
	All Participants (n=2,651)		Abortion Participants (n=931)		All Participants (n=2,468)		Abortion Participants (n=916)	
Participant Characteristics	**aOR**	***P****	**aOR**	***P****	**aOR**	***P****	**aOR**	***P****
Age	0.99	.656	0.99	.819	0.97	.003	0.99	.487
Education								
Less than high school (ref)	1.00				1.00			
High school or high school equivalency certificate	0.90	.797			0.54	<.001		
Some college	0.56	.178			0.58	<.001		
Bachelor's degree	0.89	.800			0.54	.016		
Some graduate	0.78	.501			0.60	.042		
C sordellii present at T1	2.38	.028	4.49	.003				
C perfringens present at T1					3.53	<.001	3.51	<.001
Took antibiotics for abortion								
None or a few (ref)	NA		1.00		NA		1.00	
All or almost all	NA		0.57	.207	NA		1.41	.299
Nearly half	NA		0.92	.893	NA		2.52	.114
Race–ethnicity								
White (ref)	1.00		1.00					
Latina	0.60	.286	0.82	.716				
African American	0.37	.035	0.31	.131				
Asian, Pacific Islander, or Hawaiian	0.44	.455	0.92	.937				
Other	0.85	.653	0.57	.344				
Used vaginal medication since T1	2.74	.010						
Currently pregnant	4.29	.024						
Type of abortion at or since T1								
No abortion (ref)	1.00		NA					
Medical	1.20	.702	0.78	.658				
Surgical	1.44	.399	1.00 (ref)					
Had vaginal sex since T1	1.45	.196						

	Clostridium sordellii				Clostridium perfringens			
	All Participants (n=2,651)		Abortion Participants (n=931)		All Participants (n=2,468)		Abortion Participants (n=916)	
Participant Characteristics	**aOR**	***P****	**aOR**	***P****	**aOR**	***P****	**aOR**	***P****
Alcohol use past 30 d								
None	0.91	.700						
Light (ref)	1.00							
Moderate	0.89	.836						
Heavy	1.69	.180						
Worked on farm since first visit	2.86	.009						
BMI (kg/m^2)								
Less than 18.5					1.40	.322	1.00	
18.5–24.9 (ref)					1.00		Ref†	
25.0–29.9					1.33	.160	1.17	.628
30.0–34.9					1.56	.055	1.17	.604
35 or greater					2.00	.002	1.59	.091
Used feminine product since T1					1.42	.029	1.83	.023
Took prescription medication since T1					0.73	.012		
Bleeding during abortion required intervention					NA		2.92	.001
No. of sex partners								
0 (ref)					1.00		1.00	
1					1.38	.060	1.14	.650
2 or more					2.56	.002	3.19	.017
Time since last antibiotic use								
No antibiotics (ref)					1.00			
Less than 7 d					0.98	.899		
7–13 d					0.21	.042		
14–20 d					1.72	.215		
21–30 d					0.83	.310		

aOR, adjusted odds ratio; ref, referent; T1, time 1; NA, not applicable; BMI, body mass index.

*Based on generalized estimating equation models to estimate robust standard errors after accounting for clustering at the recruitment clinic or site using an exchangeable correlation structure. Adjusted models are fully adjusted for all of the variables listed with adjusted estimates in the respective column.

† Combined BMI less than 18.5 with BMI 18.5–24.9 as a result of small cell sizes.