GYNECOLOGY

EVO100 prevents chlamydia and gonorrhea in women at high risk of infection

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BACKGROUND: According to the Centers for Disease Control and Prevention, rates of infection for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are increasing in the United States. EVO100 is an investigational antimicrobial, pH-modulating, vaginal gel with active ingredients L-lactic acid, citric acid, and potassium bitartrate that is being evaluated for the prevention of sexually transmitted infections.

OBJECTIVE: The objective of this phase 2B/3 study was to assess the efficacy and safety of EVO100 for the prevention of chlamydia and gonorrhea.

STUDY DESIGN: AMPREVENCE was a double-blinded, placebo-controlled, multicenter study based in the United States conducted over approximately 16 weeks in women at the age of 18 to 45 years who were at risk of urogenital chlamydia and gonorrhea infection. Enrolled women had been diagnosed as having and treated for chlamydia or gonorrhea ≤16 weeks before enrollment. Women received either EVO100 or placebo vaginal gel and were instructed to apply the study drug immediately before or up to 1 hour before each act of vaginal sexual intercourse. The primary and secondary endpoints were the prevention of urogenital chlamydia and gonorrhea, respectively. Exploratory outcomes include women's overall satisfaction with EVO100.

RESULTS: In total, 860 women were randomized 1:1 to receive EVO100 (n=426) or placebo (n=434), and 764 women (EVO100, n=376; placebo, n=388) were documented as using the study drug at least once. Baseline characteristics were similar between treatment arms. Overall, women had a mean age of 27.7 years (standard deviation, 6.9) and body mass index of 28.9 kg/m^2 (standard deviation, 8.0). Most women were of white (54.3% [467 of 860]) or African American (41.6% [358 of 860]) race and of non-Hispanic/Latina ethnicity (67.1% [577 of 860]). The chlamydia infection rate in EVO100 users was 4.8% (14 of 289) compared with 9.7% (28 of 290) among placebo users (*P*=.0256), representing a relative risk reduction of 50%. For gonorrhea, the infection rate was 0.7% (2 of 280) in the EVO100 arm compared with 3.2% (9 of 277) in the placebo arm (*P*=.0316), representing a relative risk reduction of 78%. Increased efficacy was observed with increased adherence, and chlamydia infection rates were significantly reduced with increased adherence in the EVO100 group compared with placebo. Across both arms, there were similar rates of all-cause adverse events (EVO100, 21.3% [80 of 376]; placebo, 20.4% [79 of 388]) and treatment-related adverse events (EVO100, 7.2% [27 of 376]; placebo, 7.5% [29 of 388]). The most common adverse events in the EVO100 arm were vulvovaginal candidiasis (5.1% [19 of 376]), vaginal discharge (3.2% [12 of 376]), and urinary tract infection (3.2% [12 of 376]) and, in the placebo arm, bacterial vaginosis (4.6% [18 of 388]), urinary tract infection (2.6% [10 of 388]), and vaginal discharge (2.6% [10 of 388]). Few women discontinued owing to adverse events in either arm (EVO100, 1.1% [4 of 376]; placebo, 1.5% [6 of 388]). No treatment-related serious adverse events were reported. Most EVO100 users (88%) were satisfied or very satisfied with EVO100 after 16 weeks of use.

CONCLUSION: EVO100 significantly reduced the risk of chlamydia and gonorrhea infections in women at high risk of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection and was well tolerated, with observed adverse events consistent with its known safety profile.

Key words: chlamydia, gonorrhea, microbicide, phase 2B/3, sexually transmitted infections, vaginal gel, vaginal pH modulator

Introduction

In 2018, the United States Centers for Disease Control and Prevention reported that *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) were the first and second most common notifiable conditions in the United States, respectively.[1] Despite the availability of the male and female condoms for prevention of sexually transmitted infections (STIs), the increasing incidence of CT and GC infection suggests that there is an urgent need for new prevention strategies, especially a method that is discrete and woman controlled. Because CT and GC infections in women are often asymptomatic and may go undetected, substantial consequences may result if left untreated.[1] Furthermore, there is a higher risk of CT or GC infection in women who were treated for CT or GC infection during the preceding several months. The subsequent infection may result from a repeat infection through an untreated partner or exposure through a new partner.

An acidic vaginal pH and colonization of lactobacilli species in the vaginal mucosa are components of the multifaceted antimicrobial defense mechanisms in the vaginal fluid, which include the production of protective bacteriostatic and bactericidal compounds by lactobacillus species.[2–6] It is thought that the naturally acidic vaginal environment may inhibit the acquisition of common STIs, including CT and GC.[7–11] A prospective case-controlled study found that independent of other factors, women with CT infections were 6 times more likely to have pH>4.5 than controls.[7] In another study, 76% of women exposed to GC through an infected partner with vaginal pH 5.0 to 6.5 subsequently developed GC infection compared with 48% of women whose vaginal pH was <5.0.[11] In the past 2

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AJOG at a Glance

Why was this study conducted?

The increasing rates of chlamydia and gonorrhea infection are urgent public health concerns; in this study, we sought to determine whether EVO100, an investigational antimicrobial, pH-modulating vaginal gel, reduces the risk of urogenital *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) in women at high risk of CT or GC infection.

Key findings

Results from our study show that EVO100 was well tolerated and was effective in reducing the risk of CT and GC infection, with significantly lower rates of CT (P=.0256) and GC (P=.0316) infection in women receiving EVO100 than placebo users.

What does this add to what is known?

There is a need for a discrete, woman-controlled method for CT and GC prevention. Several other vaginal microbicides have been developed, but have failed to protect women after further investigation. Results from our study show that EVO100 significantly reduces the risk of CT and GC infection in women at high risk of CT or GC infection.

decades, there have been several vaginal microbicidal formulations developed, and although there were promising initial preclinical studies for several agents, many have failed to protect women against STIs or HIV acquisition or lacked funding for further investigation.[12,13]

EVO100 is an investigational antimicrobial vaginal pH modulator being evaluated for the prevention of STIs. It is a novel, woman-controlled, water-based vaginal gel containing 3 active ingredients, L-lactic acid, citric acid, and potassium bitartrate. Previous studies have shown that EVO100 is well tolerated with vaginal itching and burning as the most commonly reported safety events.[14,15] Colposcopic evaluation indicated no vulvar, vaginal, or cervical signs of irritation in women who used EVO100 for 6 consecutive days.[16] It has unique pH-modulating, acid-buffering properties to maintain the acidic vaginal environment, even in the presence of alkaline semen.[17,18] Human semen is slightly alkali (pH, 7.2−8.0) and can neutralize the vaginal pH following intercourse.[19] Preclinical testing showed that EVO100 has highly effective acid-buffering properties and can buffer twice the volume of semen to maintain pH <4.5.[17] In a phase 1 dose-finding study, a single 5 g dose of EVO100 significantly reduced mean vaginal pH from baseline by −0.44 within an hour of administration and maintained reduced pH from baseline for 7 days after use. In comparison, vaginal pH in placebo users fluctuated above and below baseline pH levels throughout the 7-day study period.[14] During development, it was found that EVO100 exhibited microbicidal activity against CT and GC, without impacting the beneficial native lactobacilli, and results from a phase 1 study showed that EVO100 use reduced the concentration of *Gardnerella vaginalis*.[15,20,21] Disruption of the naturally occurring human vaginal microflora and acidic vaginal environment has been shown to be linked to an increased risk of STIs, including CT and GC.[22−27] The objective of this study was to evaluate the efficacy of EVO100 in reducing urogenital CT and GC infection in sexually active women at high risk of CT or GC infection.

Materials and Methods

Overview

In consultation with the United States Food and Drug Administration (FDA), AMPREVENCE (NCT03107377, clinicaltrials.gov) was designed as a double-blinded, placebo-controlled, randomized, phase 2B/3 trial enrolling healthy women aged 18 to 45 years who had been diagnosed as having and treated for CT or GC ≤16 weeks before enrollment to evaluate the efficacy and safety of EVO100 (formerly Amphora and ACIDFORM) over 16 weeks of use. The study protocol was approved by the Advarra (formerly known as Schulman) institutional review board.

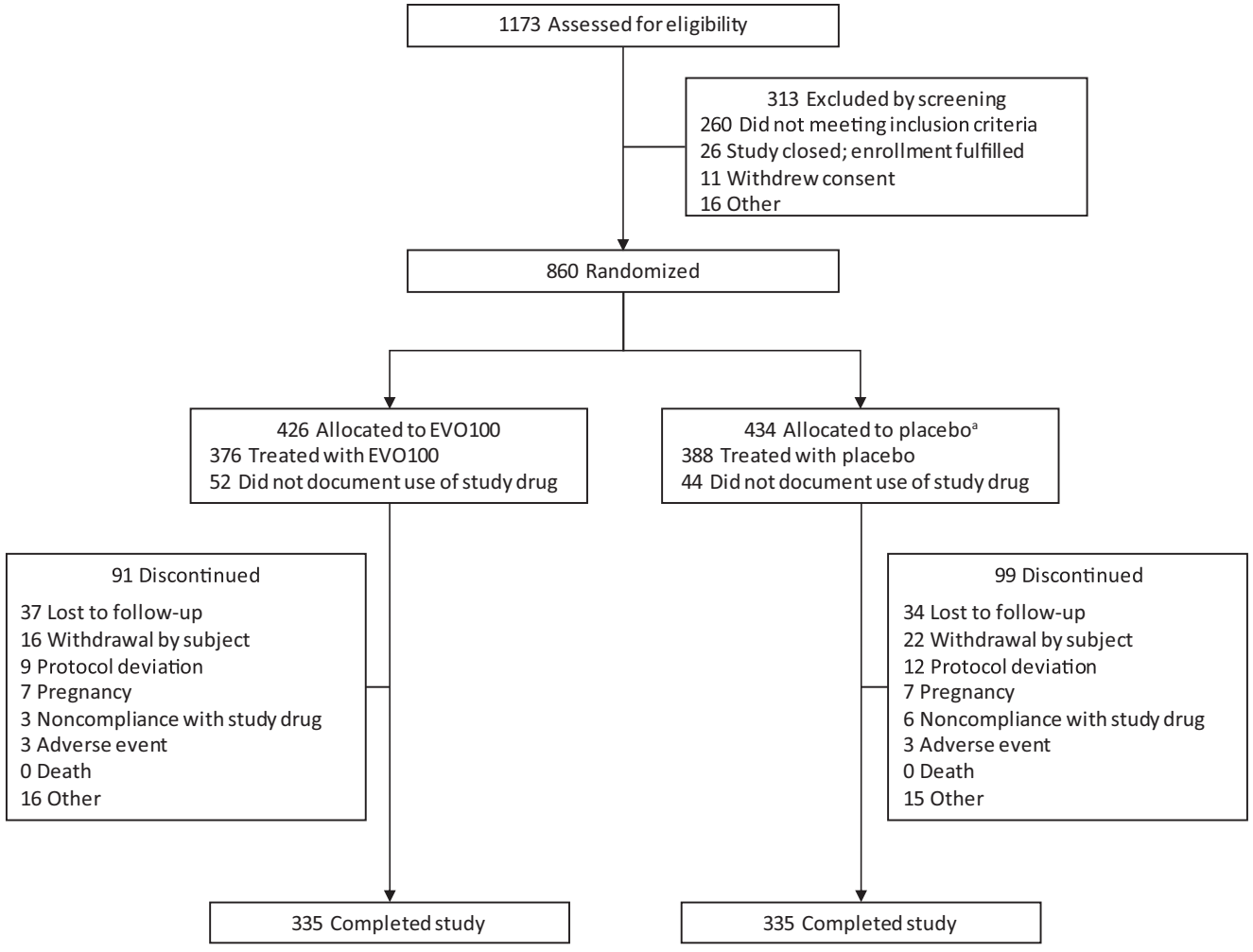
Participants, inclusion and exclusion criteria

Women were recruited through institutional review board−approved materials and database queries. Sexually active, healthy women aged 18 to 45 years who provided an informed consent were screened. Women who had documented CT or GC infection within 16 weeks preceding the enrollment visit or found to be positive at the screening visit were enrolled to ensure a study population of women who were at high risk of infection during the study period. Women were tested at screening for current CT or GC infection by nucleic acid amplification test (NAAT) via vaginal swab. Those who tested positive for CT or GC infection at screening received standard of care treatment before enrollment and were not enrolled until 3 to 4 weeks after screening (at least 21 days after treatment). Women who had signs/symptoms indicating persistence of CT or GC infection and women who were being currently treated with antibiotics with activity against CT or GC were excluded from the study. Full inclusion and exclusion criteria are detailed in Supplemental Tables 1 and 2.

Randomization, sample size determination, and product assignment

Eligible women were randomized 1:1 using an Interactive Web Response System to 2 study arms, the EVO100 vaginal gel or placebo vaginal gel after enrollment and before receiving study treatment. All investigators and women were blinded to their intervention assignment over the entire duration of the study. Blinding was not broken until all women completed the final study visit and after database lock and approval.

FIGURE 1
CONSORT diagram



[a]There were 2 women allocated to receiving placebo who inadvertently received EVO100 kits at a visit; these women were included the EVO100 group for safety analyses only.

CONSORT, Consolidated Standards of Reporting Trials.

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The sample size was determined based on the assumption that 22.5% of patients will experience at least 1 CT infection during the study period in the placebo arm and 13% in the study arm, to yield a clinically relevant treatment difference of 9.5%.[28–32] To have 80% power to detect 9.5% treatment difference with a 2-sided 5% type I error rate, a total of 506 women in the intent-to-treat (ITT) population were needed. A total sample size of 844 women was planned for this study, based on the assumption that 20% of enrolled patients would be lost to follow-up, 15% would be infected with GC (and thus not contributing to the primary endpoint of CT infection), and 5% would be ineligible for analysis owing to prohibited antibiotic use during the trial.

Study visits

At the screening visit, women provided written informed consent and were asked to return to the study site upon receiving negative CT or GC NAAT results for enrollment (visit 1). At enrollment, a swab for vaginal pH reading was collected for each woman before full gynecologic exam. In the 16-week intervention period, study visits were scheduled every 4 weeks (visits 2 to 5) to obtain repeat CT or GC NAAT, to review diary entries, and to collect adverse event (AE) and concomitant medication information. All AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v20.1. The incidence of AEs were summarized by primary system organ class, preferred term, severity, and relationship to study intervention. For visits 1 to 5, women were asked to abstain from vaginal intercourse in the 24 hours preceding the study visit. A follow-up visit (visit 6) 4 weeks after

TABLE 1
Baseline demographics and characteristics of enrolled women

	ITT		
Characteristics	EVO100 (n=426)	Placebo (n=434)	Total (N=860)
Age in y, mean (SD)	27.8 (7.1)	27.5 (6.7)	27.7 (6.9)
Race, n (%)			
White	228 (53.5)	239 (55.1)	467 (54.3)
Black or African American	185 (43.4)	173 (39.9)	358 (41.6)
American Indian/Alaska Native	3 (0.7)	2 (0.5)	5 (0.6)
Native Hawaiian or Pacific Islander	0	2 (0.5)	2 (0.2)
Asian	5 (1.2)	9 (2.1)	14 (1.6)
Other	5 (1.2)	9 (2.1)	14 (1.6)
Ethnicity, n (%)			
Hispanic or Latino	135 (31.7)	148 (34.1)	283 (32.9)
Not Hispanic or Latina	291 (68.3)	286 (65.9)	577 (67.1)
BMI at screening (kg/m^2, mean [SD])	29.1 (8.2)	28.7 (7.8)	28.9 (8.0)
Vaginal pH at screening, mean (SD)	4.5 (0.7)	4.6 (0.8)	4.5 (0.8)
Bacterial vaginosis at screening, n (%)	13 (3.1)	14 (3.2)	27 (3.1)

N=number of women in the treatment group analysis set; n=number of women in the specified category with nonmissing values.

BMI, body mass index; *ITT*, intent to treat; *SD*, standard deviation.

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the last intervention visit was scheduled for CT or GC NAAT and diary review. The protocol-defined total observation period was 20 weeks. Used and unused applicators were collected at each study visit; additional study product was issued, as needed. Questionnaires were administered at visit 5 for women to rate their overall and sexual satisfaction with the investigational product.

Treatment protocol

The study drug and placebo vaginal gel were both supplied by Evofem Biosciences, Inc. Women received a 4-week supply of the investigational product based each woman's projected usage. Women received financial compensation for their participation in the study as approved by the institutional review boards. Each prefilled single-dose applicator contained 5 g of study drug or placebo to use while engaging in vaginal sexual intercourse. Women were instructed to administer the prefilled applicator containing the study drug or placebo intravaginally immediately before or up to 1 hour before each episode of vaginal sexual intercourse for a duration of the 16-week intervention period. Women were encouraged and agreed to engage in at least 3 acts of heterosexual vaginal intercourse per month for the duration of the study. Throughout the study, women kept a diary to document sexual activity, product use, and any side effects that occurred with product use. Women were counseled according to each participating site's routine standard of care for STI prevention, which included STI prevention counseling to address a woman's individual risk factors, advice on the correct and consistent use of male condoms to prevent STIs and HIV, and condom provision per the site's standard of care.

Statistical analysis and outcome measures

The primary efficacy outcome was the incident infection of CT during the study intervention period (ie, the proportion of subjects who experienced at least 1 CT infection). The secondary outcome was the incident infection of GC during the study intervention period. Exploratory outcomes assessed overall satisfaction, product usage and adherence rates, and additional sensitivity analyses of the primary endpoint stratified by adherence rates were performed.

The study included 3 analysis populations: ITT, modified ITT (mITT), and safety. All randomized women constituted the ITT population; all randomized women who were negative for CT and GC infection at enrollment and reported use of study product before at least 1 coital event are included in the mITT population. The CT- and GC-analysis–eligible populations were subpopulations of the mITT and included women with known infection status through the end of the treatment phase, no use of prohibited antibiotic medications, and no earlier on-study GC or CT infection at time of CT or GC status determination. Women who documented any use of study product were included in the safety population.

TABLE 2
Summary of analysis-eligible populations

Population	EVO100	Placebo	Total
ITT population	426	434	860
mITT population	364 (85.4)	383 (88.2)	747 (86.9)
Women excluded from mITT population	62 (14.6)	51 (11.8)	113 (13.1)
Reason for exclusion from mITT population[a]			
Did not have negative CT or GC test result at enrollment	19 (4.5)	15 (3.5)	34 (4.0)
Did not apply any amount of study product	52 (12.2)	44 (10.1)	96 (11.2)
CT-analysis–eligible population[b]	289 (67.8)	290 (66.8)	579 (67.3)
Women excluded from CT-analysis eligibility	75 (17.6)	93 (21.4)	168 (19.5)
Reasons for exclusion from CT-analysis eligible[a]			
Unknown infection status through end of treatment phase[c]	66 (15.5)	76 (17.5)	142 (16.5)
Use of prohibited antibiotics	14 (3.3)	24 (5.5)	38 (4.4)
GC infection before CT status determination	0	0	0
GC-analysis–eligible population[b]	280 (65.7)	277 (63.8)	557 (64.8)
Women excluded from GC-analysis eligibility	84 (19.7)	106 (24.4)	190 (22.1)
Reasons for exclusion from GC-analysis eligibility[a]			
Unknown infection status through end of treatment phase[c]	78 (18.3)	97 (22.4)	175 (20.3)
Use of prohibited antibiotics	14 (3.3)	24 (5.5)	38 (4.4)
CT infection before GC status determination	0	1 (0.2)	1 (0.1)
Safety population	376 (88.3)	388 (89.4)	764 (88.8)

Values are expressed as number (percentage) unless indicated otherwise. Percentage is based on the number of women in the row category in the treatment category. The ITT population is defined as all randomized women. The mITT population is defined as all randomized women who reported use of study product and had negative CT or GC test result at enrollment.

CT, *Chlamydia trachomatis*; *GC*, *Neisseria gonorrhoeae*; *ITT*, intent to treat; *mITT*, modified intent to treat.

[a] Women may have been excluded from populations for more than 1 reason; [b] To be analysis eligible, a woman must have had known infection status through end of the treatment phase, used no prohibited antibiotic medication, and had not continued in the study after any CT or GC infection; [c] Women infected with CT or GC resulting in the conclusion of study participation before visit 5 are included in unknown infection status for the other disease.

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TABLE 3
Summary of the proportion of women with CT and GC infection during the study (mITT population)

	mITT[a]			
Population	EVO 100 (n=364)	Placebo (n=383)	Rate difference	*P* value[b]
CT-analysis–eligible population[c], n	289	290		
Women without CT infection	275 (95.2)	262 (90.3)		
Women with CT infection	14 (4.8)	28 (9.7)	−4.8	.0256
95% CI for rate and rate difference	(2.4–7.3)	(6.3–13.1)	(−9.0 to −0.6)	
GC-analysis–eligible population[c], n	280	277		
Women without GC infection	278 (99.3)	268 (96.8)		
Women with GC infection	2 (0.7)	9 (3.2)	−2.5	.0316
95% CI for rate and rate difference	(0–1.7)	(1.2–5.3)	(−4.8 to −0.2)	

Values are expressed as number (percentage) unless indicated otherwise.

CI, confidence interval; *CT*, *Chlamydia trachomatis*; *GC*, *Neisseria gonorrhoeae*; *mITT*, modified intent to treat.

[a] Percentage based on the number of women in the row category in the treatment category; [b] Two-sided *P* value based on chi-square test or Fisher exact test (if any cell count is <5); [c] To be analysis eligible, a woman must had known infection status through the end of the treatment phase, used no prohibited antibiotic medication, and had not continued in the study after any CT or GC infection.

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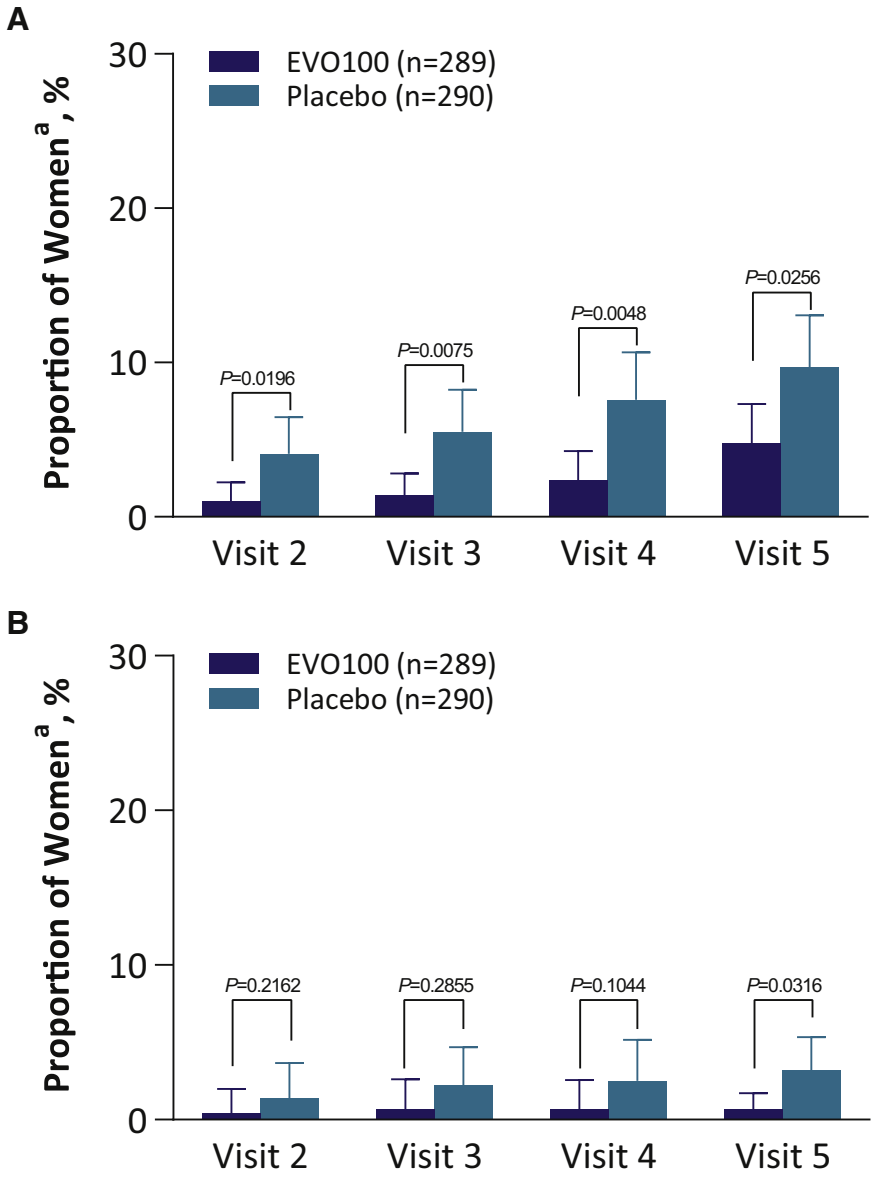
FIGURE 2
Cumulative incident of (A) CT and (B) GC infection by study visit (mITT population).



Two-sided *P* value based on chi-square test or Fisher exact test (if expected cell count is <5). The superscript letter "a" indicates the proportion of women reporting positive CT infection in CT- or GC-analysis—eligible population in each study arm.

CT, *Chlamydia trachomatis*; *GC*, *Neisseria gonorrhoeae*; *mITT*, modified intent to treat.

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The primary efficacy endpoint, the proportion of women who experienced at least 1 CT infection between the 2 intervention groups, was evaluated using a chi-square test. Similar analyses were performed for incident infection of GC. The primary analysis population was conducted in the mITT group. This was to account for some women in the ITT group who were diagnosed as having CT or GC at enrollment but test results did not become available until after randomization; therefore, those women were discontinued and not considered part of the primary analysis population. The CT- and GC-analysis—eligible population excluded women who received treatment with an antibiotic for an unrelated illness that also treats CT or GC infection, to avoid compromising the ability to detect the impact of the study drug on CT or GC prevention. Overall adherence with product use were analyzed using diary data. Additional sensitivity analyses on the mITT population examined whether the level of CT or GC infection between treatment groups differs by adherence rates. Women's overall satisfaction with EVO100 was summarized using frequency and percentage. Condom usage rates and its effect on CT and GC infection rates were also explored.

Results

Enrollment, disposition, and participant characteristics

AMPREVENCE enrolled 860 women across 51 United States—based study sites starting November 2017 and was completed in August 2019 (Supplemental Table 3). Women were randomized 1:1 into 2 arms, EVO100 (n=426) and placebo (n=434) (Figure 1). Baseline demographics were similar between treatment arms (Table 1) as were analysis populations (Table 2). Overall, women had a mean age of 27.7 years (standard deviation, 6.9) and body mass index of 28.9 kg/m^2 (standard deviation, 8.0). Most women were of white (54.3%) or African American (41.6%) race and of non-Hispanic/Latina ethnicity (67.1%). The discontinuation rate was similar between the 2 arms (EVO100, 21.4%; placebo, 22.8%). Overall, the most frequent reason for study discontinuation was lost to follow-up (71 of 860 [8.3%]), withdrawal by subject (38 of 860 [4.4%]), and protocol deviation (21 of 860 [2.4%]).

Primary and secondary efficacy outcomes

Among the 747 women included in the mITT population (EVO100, n=364; placebo, n=383), 579 women were included in the primary efficacy analysis (EVO100, n=289; placebo,

TABLE 4
Summary of treatment adherence (mITT population)

Characteristic	mITT		
	EVO100 (n=364)	Placebo (n=383)	Total (N=747)
Number of coital events, mean (SD)	15.7 (13.5)	16.3 (15.8)	16.0 (14.7)
Study product adherence[a,b]			
0%	12 (3.3)	18 (4.7)	30 (4.0)
>0% to <20%	10 (2.7)	9 (2.3)	19 (2.5)
≥20%	20 (5.5)	16 (4.2)	36 (4.8)
≥40%	28 (7.7)	27 (7.0)	55 (7.4)
≥60%	49 (13.5)	49 (12.8)	98 (13.1)
≥80%	127 (34.9)	151 (39.4)	278 (37.2)
100%	114 (31.3)	107 (27.9)	221 (29.6)
Missing	4	6	10

Values are expressed as number (percentage) unless indicated otherwise. N=number of women in the treatment group analysis set; n=number of women in the specified category.

mITT, modified intent to treat; *SD*, standard deviation.

[a] From women's diary entries, adherence was calculated as the ratio of the number of times the product was properly used to all coital events recorded during the treatment phase; [b] For frequency result of adherence, each group was deemed mutually exclusive.

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n=290). A total of 168 women were excluded from the primary efficacy analysis owing to unknown infection status through the end of treatment phase or use of prohibited antibiotics. Among CT-analysis–eligible women, 4.8% of women (14 of 289) receiving EVO100 compared with 9.7% of women (28 of 290) women receiving placebo gel experienced CT infection during the study, representing a significant reduction in the relative risk of infection by 50% (*P*=.0256) with EVO100 use (Table 3). Throughout the study at each visit, the cumulative incident CT infection rate was significantly lower in women treated with EVO100 compared with women treated with placebo (Figure 2, A). Among GC-analysis–eligible women, there was significantly lower incident GC infection rate in the EVO100 arm (0.7% [2 of 280]) compared with the placebo arm (3.2% [9 of 277]), which represented a significant relative risk reduction of 78% (*P*=.0316) (Table 3). At each study visit, women treated with EVO100 had lower rates of GC infection compared with women treated with placebo (Figure 2, B).

Measurement of treatment adherence

2Overall, women reported a mean of 16 (standard deviation, 14.7) coital events (EVO100, 15.7 [standard deviation, 13.5]; placebo, 16.3 [standard deviation, 15.8]) during the 16-week active treatment phase. As assessed from women's diaries, adherence was similar between both treatment arms in the mITT population; 66% of women (241 of 364) using EVO100 and 67% of women (258 of 383) using placebo had treatment adherence of ≥80% (Table 4). To examine the proportion of women with CT infection during the study based on adherence rates, additional sensitivity analyses in the CT-analysis–eligible population showed EVO100 users with 100% adherence were significantly less likely to acquire CT infection compared with women using placebo (2.3% vs 16.9%; *P*=.0012). Among women with adherence rates of ≥20%, ≥40%, ≥60%, or ≥80%, no significant differences were found in the proportion of women with CT infections between women treated with EVO100 and placebo. Additional sensitivity analyses on GC-analysis–eligible population showed no significant differences of GC infection between women using EVO100 (1 of 87) or placebo (0 of 70) who were 100% adherent or among those with ≥20%, ≥40%, ≥60%, or ≥80% adherence rates.

Impact of condom usage on *Chlamydia trachomatis* or *Neisseria gonorrhoeae* infection

Women also tracked condom usage for each act of intercourse in their eDiaires. The mean condom usage rate, calculated as the ratio of the number of coital acts with a male condom to the total number of coital acts during study treatment, was similar in both arms (EVO100, 24.5%; placebo, 26.7%). CT or GC infection rates by treatment group and condom usage (none, low, high) are presented. For this analysis, low condom use was defined as women with a rate that was ≤50th percentile of all condom users. Among CT- and GC-analysis–eligible women, EVO100 was associated with a significantly reduced rate of CT infection (2.8% vs 6.9%; *P*=.0069) and GC infection (0.7% vs 2.9%; *P*=.0486) compared with placebo when no condom usage was reported (Table 5).

TABLE 5
Sensitivity analysis of CT or GC infection by condom usage rate (mITT population)

	mITT[a]		
Characteristic	EVO100 (n=364)	Placebo (n=383)	*P* value[b]
CT-analysis–eligible population, n[c]	289	290	
No condom usage			
No infection	171 (59.2)	139 (47.9)	.0069
Infection	8 (2.8)	20 (6.9)	
Low condom usage			
No infection	52 (18.0)	64 (22.1)	.4639
Infection	2 (0.7)	6 (2.1)	
High condom usage			
No infection	51 (17.6)	59 (20.3)	.6644
Infection	3 (1.0)	2 (0.7)	
GC-analysis–eligible population, n[c]	280	277	
No condom usage			
No infection	174 (62.1)	143 (51.6)	.0486
Infection	2 (0.7)	8 (2.9)	
Low condom usage			
No infection	52 (18.6)	66 (23.8)	1.0000
Infection	0	1 (0.4)	
High condom usage			
No infection	51 (18.2)	59 (21.3)	N/A
Infection	0	0	

Values are expressed as number (percentage) unless indicated otherwise. Low condom use defined as women with a rate of >0 and ≤50th percentile of condom usage across all women.

CT, *Chlamydia trachomatis*; *GC*, *Neisseria gonorrhoeae*; *mITT*, modified intent to treat; *N/A*, not assessable.

[a] Percentage based on the number of women in the row category in the treatment category; [b] Two-sided *P* value based on chi-square test or Fisher exact test (if any expected cell count was <5); [c] To be analysis eligible, a woman must had known infection status through the end of the treatment phase, used no prohibited antibiotic medication, and had not continued in the study after any CT or GC infection.

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Safety

Of 860 women randomized, 764 women were included in the safety population (EVO100, n=376; placebo, n=388). Overall, 20.8% of women experienced an AE during the study (Table 6). There were similar rates of all-cause AEs between the 2 arms (EVO100, 21.3%; placebo, 20.4%) and treatment-related AEs (EVO100, 7.2%; placebo, 7.5%). In total, 4 women (1.1%) receiving the study drug and 6 women (1.5%) receiving placebo withdrew from the study owing to AEs.

The most common AEs reported by women in the EVO100 arm were vulvovaginal candidiasis (5.1%), vaginal discharge (3.2%), and urinary tract infection (3.2%) and bacterial vaginosis (4.6%), urinary tract infection (2.6%), and vaginal discharge (2.6%) in the placebo arm. Among all women reporting an AE, most AEs were considered mild (EVO100, 10.6% [40 of 376]; placebo, 7.7% [30 of 388]) or moderate (EVO100, 9.8% [37 of 376]; placebo, 11.6 [45 of 388]).

A total of 56 women (7.3%) experienced a treatment-related AE during the study (EVO100, 27 of 376 [7.2%]; placebo 29 of 388 [7.5%]). For women receiving EVO100, the most frequently reported treatment-related AEs were vulvovaginal candidiasis (13 of 376 [3.5%]), vulvovaginal discomfort (5 of 376 [1.3%]), bacterial vaginosis (4 of 376 [1.1%]), and vaginal discharge and vulvovaginal burning sensation (each 3 of 376 [0.8%]). For placebo users, the most frequently reported treatment-related AEs were bacterial vaginosis (9 of 388 [2.3%]), urinary tract infection (7 of 388 [1.8%]), vulvovaginal candidiasis (7 of 388 [1.8%]), vaginal discharge (4 of 388 [1.0%]), and vulvovaginal discomfort (3 of 388 [0.8%]).

Overall, there were 6 women who reported AEs as "severe" in intensity (EVO100, <1% [2 of 376]; placebo, 1.0% [4 of 388]). There was 1 EVO100 user who experienced a life-threatening AE (diabetic ketoacidosis), but this was assessed to be unlikely related to treatment. There were no deaths reported in

TABLE 6
Summary of AEs occurring in ≥2% of women (safety population)

Characteristic	Safety[a] EVO100 (n=376)	Placebo (n=388)	Total (N=764)
Any AE[b]	80 (21.3)	79 (20.4)	159 (20.8)
Gastrointestinal disorders	3 (0.8)	13 (3.4)	16 (2.1)
Infections and infestations[c]	50 (13.3)	49 (12.6)	99 (13.0)
Bacterial vaginosis	11 (2.9)	18 (4.6)	29 (3.8)
Urinary tract infection	12 (3.2)	10 (2.6)	22 (2.9)
Vulvovaginal candidiasis	19 (5.1)	8 (2.1)	27 (3.5)
Reproductive and breast disorders[c]	29 (7.7)	21 (5.4)	50 (6.5)
Vaginal discharge	12 (3.2)	10 (2.6)	22 (2.9)
Vulvovaginal discomfort	8 (2.1)	4 (1.0)	12 (1.6)
Any serious AEs[a,b]	2 (0.5)	3 (0.8)	5 (0.7)
Discontinuation owing to an AE[a,b]	4 (1.1)	6 (1.5)	10 (1.3)

Values are expressed as number (percentage) unless indicated otherwise. N=number of women in the treatment group analysis set; n=number of women in the specified category with nonmissing values.

AE, adverse event.

[a] Percentage based on the number of women in the row category within each treatment category; [b] AEs were coded by the Medical Dictionary for Regulatory Activities (version 20.1) by system organ class and preferred term; [c] Totals for the number of women at a higher level may not equal the sum of lower levels because women may have reported 2 or more different AEs within the higher level category.

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either arm. The incidence of serious AEs was low (EVO100, <1% [2 of 376]; placebo, <1% [3 of 388]), and all serious AEs were unlikely related to treatment.

Overall satisfaction with EVO100

The satisfaction questionnaire was given at visit 5 to assess women's satisfaction in 3 categories: (1) satisfaction with the study product, (2) likelihood of recommending this method to others considering such a product, and (3) the likelihood of continuing with the use of the product if it were available after the study. Of the 364 women assigned EVO100 in the mITT population, 273 women provided answers to the satisfaction questionnaire administered at visit 5. After 16 weeks, 88% of women (241 of 273) reported being "very satisfied" or "satisfied" with the study drug (Figure 3). Among respondents, 91% of women (249 of 273) reported "very likely" or "likely" to recommend the study drug to others, and 81% of women (222 of 273) reported that they would be "very likely" or "likely" to continue with EVO100.

Comment

Principal findings

Results from this randomized, phase 2B/3 contraceptive study showed that EVO100 significantly reduced the risk of urogenital CT and GC infections in women at high risk of CT or GC infection. AMPREVENCE met its primary and secondary efficacy endpoints, with significantly lower CT and GC infection rates in women receiving EVO100 than placebo users.

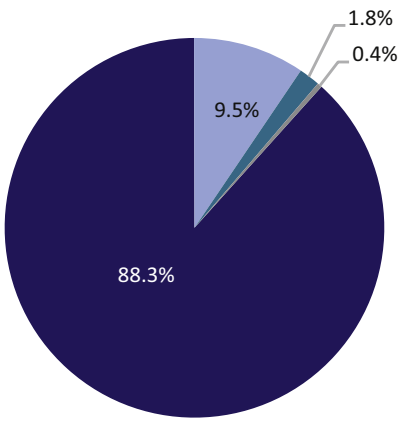
Results

Results from our study suggest a positive association between adherence and efficacy; women who were more compliant (≥80% adherence) were significantly less likely to experience CT infection. There were no new or unexpected safety events. Overall, fewer than 2% of women discontinued owing to an AE and all serious AEs were unlikely to be related to treatment. Among women receiving EVO100, most AEs reported were mild or moderate in severity. Most women surveyed reported being satisfied with EVO100 and were likely to continue using it after the study, even among women who discontinued with the study early (data not shown).

Clinical implications

CT infection has remained the most prevalent of all STIs in the United States, and as of 2018, 97.4% of all reported cases of CT were among women aged 15 to 44 years.[1] However, because CT is usually asymptomatic, prolonged infections could lead to adverse reproductive health complications, continue transmission to sexual partners, facilitate the transmission of HIV, and be passed from mother to infants in delivery.[33,34] The resulting burden of disease and associated risks is the main reason that CT infection is estimated to be the costliest of all nonviral STIs.[35] Like CT, GC infections are often asymptomatic and a major cause of pelvic inflammatory disease in the United States, which may lead to serious reproductive outcomes in women.[1] In addition, owing to progressive antibiotic resistance, GC is becoming increasingly difficult to treat, and dual therapy with ceftriaxone and

FIGURE 3
Women's satisfaction with EVO100 at visit 5[a] (modified intent-to-treat population)



Overall satisfaction with study treatment was only evaluated in EVO100 treatment arm. The superscript letter "a" indicates that percentages were calculated based on the respondents to the questionnaire at visit 5.

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azithromycin is the only recommended treatment for GC.[33] To control these STIs, new tools and systems for prevention and treatment are needed. In this study, women were aware of their risk of CT or GC infection and that half of the participants received placebo; however, condom usage was not reported in approximately 75% of acts of intercourse. EVO100, as a woman-controlled, on-demand antimicrobial vaginal gel may meet the needs of women who desire to be in control of a protection method for STI prevention.

Strengths and limitations

The strengths of this trial included its rigorous study design developed in collaboration with the FDA and the inclusion of a large number of women at risk of infection. In women, high rates of CT and GC infection in the months after treatment for infection have been observed either as a result of infection from an untreated partner or exposure through a new partner.[36] The study limitations include smaller sample sizes in the GC subgroups owing to fewer cases of GC infections. Relying on self-reports of coital frequency may also be a limitation. Although use of the diaries is helpful for collection of study data, it may encourage compliance and efficacy that may be higher in the "real-world" population outside of the setting of a clinical trial.

Conclusions

Although studies have found an association between acquisition of STIs such as CT and GC with higher vaginal pH, this prospective, randomized study evaluates the use of a vaginal pH-modulating gel for the prevention of CT and GC infection. In this study, EVO100 significantly reduced the risk of CT and GC infections in women at high risk of CT or GC infection, was safe, and was highly acceptable among users. EVO100 has the potential of fulfilling an unmet need in women's sexual health as a new on-demand, woman-controlled option that reduces the risk of urogenital CT and GC infections. ■

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This clinical trial was registered at www.ClinicalTrials.gov as NCT03107377—phase 2B/3 double-blinded placebo-controlled efficacy trial of Amphora Gel for the Prevention of Acquisition of Urogenital *Chlamydia Trachomatis* Infection. The URL can be found at https://www.clinicaltrials.gov/ct2/show/study/NCT03107377. Date of registration: April 4, 2017. Date of initial patient enrollment: December 28, 2017.

The AMPREVENCE study design and statistical analysis was designed in consultation with the United States Food and Drug Administration.

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SUPPLEMENTAL TABLE 1
Complete inclusion criteria

A woman was eligible for inclusion in the study if all of the following criteria were met:	
1	Healthy women between 18 and 45 y of age, inclusive
2	Ability to understand the consent process and procedures
3	Women agreed to be available for all study visits
4	Written informed consent in accordance with institutional guidelines
5	Negative pregnancy test
6	Negative CT and GC NAAT at screening or positive CT or GC NAAT and received standard of care treatment before enrollment
7	Agreed to use a woman-controlled method of contraception that is not directly delivered to the vaginal mucosa (with the exception of a vaginal ring) throughout the duration of the study, such as oral contraceptives, birth control implants, intrauterine devices, or tubal ligation. Condom use only was not an acceptable form of contraception for this study.
8	Able and willing to comply with all study procedures
9	Documented (as part of a retrievable medical record) CT or GC infection within 16 wk before enrollment. Acceptable documentation included: a. Lab reports confirming CT or GC infection or b. Third party clinic note confirming previous CT or GC infection and indicating the date of diagnosis and/or date of treatment
10	Reported vaginal sexual intercourse with a male partner at least 3 times per mo in the previous mo and anticipated vaginal sexual intercourse regularly for the duration of the study
11	Agreed to abstain from douching or any form of vaginal suppository use (other than investigational product) during course of study

CT, *Chlamydia trachomatis*; *GC*, *Neisseria gonorrhoeae*; *NAAT*, nucleic acid amplification test.

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SUPPLEMENTAL TABLE 2
Complete exclusion criteria

Women who met any 1 of the following criteria were ineligible for participation in the study:	
1	Participation in any study with an investigational compound or device within 30 d before signing informed consent
2	In the opinion of the investigator, had a history of substance or alcohol abuse in the last 12 mo
3	In the opinion of the investigator, had issues, conditions, or concerns that may have compromised the safety of the woman, impacted the woman's compliance with the protocol requirements, or confounded the reliability of the data acquired
4	Was an Evofem, ICON GPHS, or clinical site employee regardless of direct involvement in research activities, or their close relative
5	Pregnant (or actively trying to become pregnant) or breastfeeding
6	Women who had undergone a total hysterectomy (had uterus and cervix removed)
7	Inability to provide informed consent
8	Has a history or expectation of noncompliance with medications or intervention protocol
9	Had engaged in sexual vaginal intercourse or douching or used any form of vaginal suppository or intravaginal device (with the exception of contraceptive vaginal ring or tampons) for 24 h before enrollment (may be enrolled at a later date if all other criteria were met)
10	Menstruating at enrollment (may be enrolled at a later date if all other criteria were met)
11	Was currently being treated, or had been treated, for a period of 21 d before enrollment, with specific antibiotics known to be used for the treatment of CT or GC: • Azithromycin • Erythromycin • Tetracycline • Minocycline • Doxycycline • Levofloxacin • Ofloxacin • Ceftriaxone • Cefixime
12	In the opinion of the Investigator, had signs/symptoms that indicate persistence of chlamydia or gonorrhea infection diagnosed at screening, new interval infection, and/or a failure to comply with or complete the prescribed treatment regimen following a positive screening NAAT
13	Women who regularly used douches, vaginal medications, products, or suppositories
14	Women who are currently using contraceptive products that are directly delivered to the vaginal mucosa, such as diaphragms, contraceptive gels, or any vaginally applied or inserted products containing N-9
15	Children, pregnant women, prisoners, and other vulnerable populations

CT, *Chlamydia trachomatis*; *GC*, *Neisseria gonorrhoeae*; *N-9*, nonoxynol-9; *NAAT*, nucleic acid amplification test.
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SUPPLEMENTAL TABLE 3
Participating sites by state

State	Number of sites (N=51)	Number of women (N=860)
Alabama	2 (3.9)	24 (2.8)
Arizona	3 (5.9)	61 (7.1)
California	5 (9.8)	155 (18.0)
Colorado	1 (2.0)	6 (0.7)
Connecticut	1 (2.0)	45 (5.2)
Florida	6 (11.8)	152 (17.7)
Georgia	3 (5.9)	40 (4.7)
Idaho	1 (2.0)	31 (3.6)
Illinois	1 (2.0)	4 (0.5)
Louisiana	2 (3.9)	21 (2.4)
Michigan	1 (2.0)	8 (0.9)
Mississippi	2 (3.9)	13 (1.5)
Nevada	1 (2.0)	4 (0.5)
New Mexico	1 (2.0)	8 (0.9)
North Carolina	3 (5.9)	18 (2.1)
Ohio	1 (2.0)	15 (1.7)
Pennsylvania	2 (3.9)	73 (8.5)
South Carolina	1 (2.0)	6 (0.7)
Tennessee	2 (3.9)	32 (3.7)
Texas	11 (21.6)	132 (15.3)
Virginia	1 (2.0)	12 (1.4)

Values are expressed as number (percentage) unless indicated otherwise.

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