

Pilot Study to Evaluate Compliance and Tolerability of Cranberry Capsules in Pregnancy for the Prevention of Asymptomatic Bacteriuria

Deborah A. Wing, MD, MBA,¹ Pamela J. Rumney, RNC,¹ Sasha Hindra,¹ Lizette Guzman,¹ Jennifer Le, PharmD,^{2,3} and Michael Nageotte, MD²

Abstract

Objectives: To evaluate the compliance with and tolerability of daily cranberry capsule ingestion for asymptomatic bacteriuria (ASB) prevention in pregnancy.

Design: A total of 49 pregnant women from two sites were randomly assigned to cranberry or matching placebo, two doses daily, at gestational ages less than 16 weeks. Patients were followed monthly for urinary tract infection until delivery. Up to seven monthly visits were scheduled for each patient. Delivery data were evaluated.

Results: Of 38 evaluable patients, the mean compliance rate over the study period was 82% (range, 20%–100%). This compliance rate and the 74% of patients achieving good ($\geq 75\%$) compliance were similar between those who received cranberry capsules and placebo. Compliance evaluation revealed that most patients stopped capsule consumption after 34–38 weeks of participation. Multivariate logistic regression and longitudinal analysis showed a significant interaction time effect with cranberry treatment. However, cranberry consumption was not a significant predictor of gastrointestinal intolerance or study withdrawal. Although 30% of patients withdrew for various reasons, only 1 withdrew because of intolerance to the cranberry capsules. Loss to follow-up was mostly due to provider change (9 of 49 [18%]) and therapy disinterest (4 of 49 [8%]). Seven cases of ASB occurred in 5 patients: 2 of 24 (8%) in the cranberry group and 3 of 25 (12%) in the placebo group. No cases of cystitis or pyelonephritis were observed.

Conclusion: One third of pregnant women could not complete the study protocol for various reasons. Compliance with and tolerability of cranberry capsule ingestion appear good; these capsules provide a potentially effective means to prevent ASB in pregnancy. Further studies with large samples are necessary to confirm the findings.

Introduction

ASYMPTOMATIC BACTERIURIA (ASB) in pregnancy is associated with a variety of adverse perinatal outcomes, including preterm delivery and low birthweight.^{1–4} A primary goal in the detection and treatment of ASB during pregnancy is the reduction of risk of acute pyelonephritis and preterm birth.^{5–8} With an estimated prevalence of 5%–12% of asymptomatic bacteriuria in pregnancy,^{5–8} there is an unmet need for ASB prevention.

This study was designed to evaluate an alternative vehicle for administering daily cranberry as encapsulated powder to pregnant women. It builds on the authors' experience evaluating daily cranberry juice ingestion in pregnancy for the same purpose.⁹ That study found a trend toward fewer

urinary tract infections (UTIs) in women who received multiple daily doses of cranberry juice cocktail compared with those who received placebo. More women in the once-daily dosing group and placebo group were likely to have at least one UTI compared with the multiple-daily-dosing group (incidence rate ratio, 0.85 [95% confidence interval (CI), 0.34–2.08] for single daily dosing versus 0.43 [95% CI, 0.14–1.39] for multiple daily dosing).⁹

The mechanism by which cranberry may prevent UTI is unknown. However, a growing body of evidence suggests that proanthocyanidins or condensed tannins, components in many berry products, inhibit the adhesion of piliated enteric bacteria, such as *Escherichia coli*, to the uroepithelium.^{10,11} The current study used encapsulated cranberry powder that mimicked the dosing used in a previous investigation

¹Department of Obstetrics-Gynecology, University of California, Irvine, Orange, CA.

²Miller Children's and Women's Hospital, Long Beach, Long Beach, CA.

³Skaggs School of Pharmacy, University of California, San Diego, San Diego, CA.

conducted by this group in which cranberry juice was given daily.⁹ Previous pilot study results revealed that compliance and tolerability were limited, primarily because of gastrointestinal symptoms related to daily juice consumption. Because of the greater than 30% dropout rate,⁹ it may be possible that compliance with and tolerability of encapsulated powder from desiccated cranberries would be better than with frequent daily dosing of cranberry juice cocktail. The primary objective of this pilot randomized, placebo-controlled study was to evaluate compliance with and tolerability of cranberry capsules.

Material and Methods

Study population

Eligible healthy, pregnant women seeking prenatal care with non-anomalous fetuses between 12 and 16 weeks of gestation were identified at the University of California, Irvine, Medical Center (UCIMC) or Miller Children's and Women's Hospital, Long Beach, California (LBMMC). The institutional review boards of both institutions approved the study. Participants were excluded from analysis if they had previous underlying medical conditions, including diabetes mellitus, renal failure, sickle cell disease, chronic hypertension, or chronic renal disease; had previous or current antimicrobial therapy at the time of screening or within 2 weeks of screening; or had known urologic abnormalities. Each participant also had a pretreatment urine culture performed to ensure the absence of ASB. All participants provided written informed consent.

Study methods

Each participant was seen monthly in conjunction with her prenatal care visits by a research coordinator who asked about compliance, tolerance, and side effects of the daily cranberry capsules. Participants were followed through delivery and the immediate puerperium. For participants reporting poor compliance or tolerance, more frequent research coordinator contact or clinic follow-up was offered. In addition, participants maintained a daily dietary diary in which they recorded the total number of capsules they consumed and recorded side effects.

During follow-up visits, a clean-catch urine specimen was collected for dipstick urinalysis. If the specimen was positive for leukocyte esterase and nitrites, reflex microscopy, urine culture, and pathogen susceptibility were performed. Participants were queried about symptoms of urinary tract infection or preterm labor.

All participants were instructed to ingest two cranberry capsules, biochemically equivalent to one 250-mL dose of cranberry juice cocktail, or placebo capsules twice daily (four total capsules per day) until delivery; one dose of two capsules in the morning and a second dose of two capsules in the evening with meal was the treatment regimen.

Participants were instructed not to consume any cranberry products other than those for the study. They were educated about UTIs and hygiene practices to aid in the prevention of UTIs, including adequate fluid intake, frequent voids, and voiding after coitus. In addition, participants were educated about the importance of compliance with recommended therapies.

Randomization

Through use of a computer-generated randomization table, the women were randomly assigned to cranberry or placebo capsules. Randomization was stratified by site. An individual not associated with the study prepared the bottles of capsules in accord with the randomization sequence. The identities of the treatment assignments were not known to the participants, research coordinators, or investigators. Unblinding did not occur until termination of the investigation.

Study product

The cranberry capsule product used in this study was TheraCran® (Theralogix, Sharon Hill, PA); it contained dried cranberry powder from *Vaccinium macrocarpon* Aiton berries. These were provided by Ocean Spray Cranberries Inc. (Lakeville-Middleboro, MA), the subcontractor for the juice products used for the previously conducted trial by our group.⁹ Each dose comprised two cranberry capsules. This was equivalent to one 250-mL dose of cranberry juice cocktail, which was used in the previous study.⁹ One TheraCran® capsule minimally contained 16.25 mg of proanthocyanidin; two capsules contained 32–34 mg of proanthocyanidin using the Ocean Spray (OSC) propriety *N,N*-dimethylacetamide method¹² with a modified wash step of 50% ethanol. Theralogix, in conjunction with Ocean Spray Cranberries, Inc., provided the matching placebos for this investigation. The placebo capsules were designed to mimic the flavor (including sugar and acid profile) and color of the cranberry capsules. The placebos contained no cranberry ingredients.

Outcome measures

The primary clinical outcome measures were compliance and tolerability. Compliance was measured objectively by capsule counts at the monthly visits and subjectively by patient self-reporting. Participants reported daily capsule consumption, with or without meals. The compliance rate was calculated by capsule count for each visit. Compliance rates of 75% or greater and 100% or less were used as the target rate for this investigation; compliance was evaluated at each study visit. Once a participant withdrew or was discontinued from the study, evaluation of compliance ceased at that time. Tolerability was evaluated by tabulating the side effects of daily cranberry capsules ingestion with patient evaluation per visit and asking the participants about symptoms of nausea, gastrointestinal distress, intolerance to taste, and loss of appetite. Gastrointestinal intolerance was defined collectively as heartburn, constipation, diarrhea, nausea, vomiting, stomachache, and loss of appetite. The reasons for which participants did not complete the study protocol were tabulated. Reasons were directly related to the study design and indirectly related events, such as change of insurance that resulted in relocation of medical care.

The secondary outcome measure was the number of cases of bacteriuria, defined as having a urine culture with at least 100,000 colony-forming units of a single uropathogen per milliliter. ASB was defined as a urine culture consistent with bacteriuria without symptoms. Acute cystitis was diagnosed in participants with symptoms of dysuria, urinary frequency and/or urinary urgency, and urine cultures consistent with

bacteriuria. Acute pyelonephritis was diagnosed in participants with flank pain, fever (temperature >100.4 °F), chills, and nausea and/or vomiting, with urinalyses and/or urine cultures indicating bacteriuria. Pyuria was not detected or defined. Treatment failure was defined as any case of bacteriuria, acute cystitis, or acute pyelonephritis. Women with treatment failure continued taking the cranberry or placebo capsules through delivery.

Standardized treatments were used for ASB, acute cystitis, and acute pyelonephritis. Generally for ASB and acute cystitis, 500 mg oral cephalexin four times daily for 7 days was prescribed; for acute pyelonephritis, 1 or 2 g intravenous cefazolin four times daily was to be given until the patient had no fever for 2 days. Parenteral gentamicin could have been added on the basis of clinical response. Participants with acute pyelonephritis were subsequently treated with 500 mg oral cephalexin four times daily to complete a minimum of 10 days of antibiotic therapy. Any participant with ASB or a symptomatic urinary tract infection continued with cranberry or placebo capsules during treatment. Cultures were repeated within 2 weeks of treatment completion to assess eradication of bacteria. It was anticipated that 20%–30% of women would require a second course of a different antibiotic based on susceptibility testing. At each monthly visit, compliance was assessed by using dietary diaries and a self-reported assessment of percentage compliance with the dosing schedule.

Sample size and data analysis

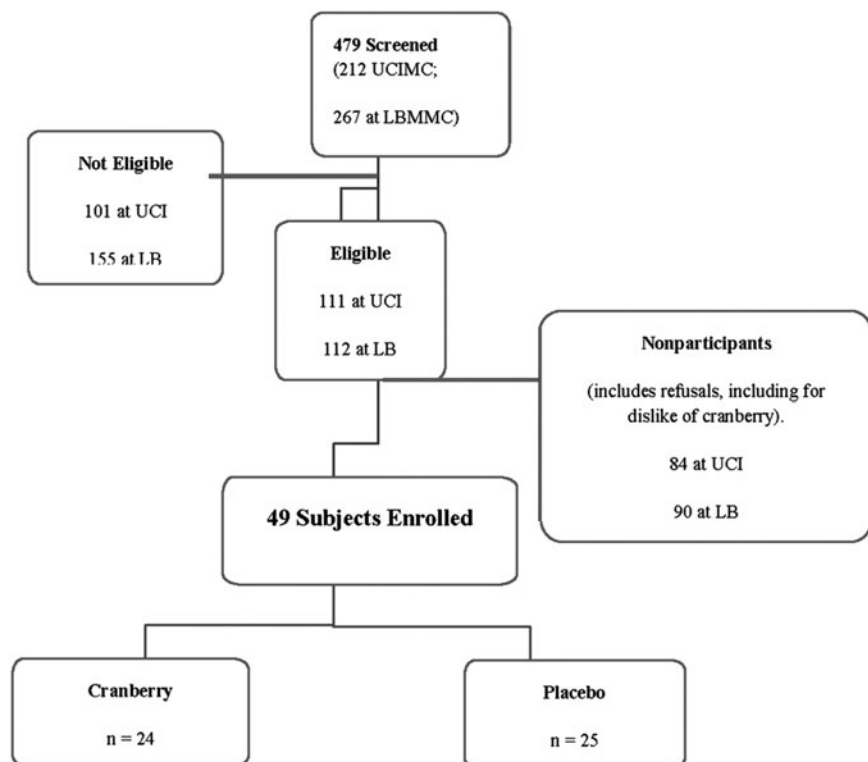
Because preliminary data were lacking about pregnant women's abilities to comply with and tolerate daily cranberry capsule ingestion, a pilot trial was performed to gen-

erate preliminary data for the design of a large-scale clinical trial. An efficacy trial was not feasible with the available resources. Additional outcome measures included effective resolution of ASB with antibiotic treatment, side effects, rates of ASB recurrence, and preterm delivery with its associated neonatal morbidities. Toxicities, side effects, tolerability, and compliance were reviewed.

All data were entered into an Excel® database (Microsoft Corp., Redmond, WA) and reformatted for analysis in SPSS Statistics software, version 21 (IBM, Armonk, NY). Data were compared between the two randomized groups—cranberry capsules and placebo—using the *t*-test or Mann-Whitney U rank-sum test for continuous variables and the chi-square or Fisher exact test for categorical variables. The data analyses were performed on an intention-to-treat basis. A significance level of 0.05 for a two-sided test was assumed when the results were calculated.

The Mantel-Haenszel test was used to estimate the common odds ratio (OR) to test for significant association between cranberry consumption and achieving 75% or greater compliance or study withdrawal. Multivariate and longitudinal analyses were conducted to evaluate the time effects on cranberry consumption on four dependent variables: compliance rate, achievement of good compliance (defined as $\geq 75\%$), gastrointestinal intolerance, and study withdrawal. Multivariate linear (for compliance rate) and logistic (for all other binomial dependent variables) analyses were conducted. The fixed and random effects on the dependent variables were analyzed longitudinally by using a multivariable mixed-effects model and generalized estimating equations (GEEs). Both linear and profile models were used to assess changes in these dependent variables over the surveillance period until study withdrawal or

FIG. 1. Patient population. “Screened” refers to total number of patients screened for study. “Not eligible” refers to number of patients not meeting criteria for study. “Eligible” refers to number of patients meeting criteria for study. “Nonparticipants” refers to women who were eligible for study but did not participate (this includes those who declined and those who disliked cranberries). “Subjects enrolled” refers to the total number of participants in study. “Cranberry” refers to number of participants assigned to cranberry capsules. “Placebo” refers to number of participants assigned to placebo. LBMMC and LB, Long Beach Memorial Medical Center; UCIMC and UCI, University of California Irvine Medical Center.



infant delivery. The final model selected to describe the longitudinal data was based on the lowest values using the Akaike information and corrected quasi-likelihood under independence model criteria. The effects of gastrointestinal intolerance on compliance and study withdrawal were also evaluated by using a multivariable mixed-effects model and GEEs.

Results

From 2009 to 2012, a total of 49 women were enrolled in this pilot investigation, with 27 participants at UCIMC and

22 participants at LBMMC (Fig. 1). Demographic characteristics did not differ between participants randomly assigned to cranberry (*n*=24) and those assigned to placebo (*n*=25) capsules (Table 1). Most participants were Hispanic (67%) and received public funding (80%). One fourth of participants had a history of UTIs.

Compliance was not evaluable in 11 participants because those participants did not bring bottles for capsule count or the daily diary for self-reporting to the study visits. Of the remaining 38 participants, the mean compliance rate over the treatment period was 82% (range, 20%–100%). The compliance rate and percentage of participants achieving 75% or greater compliance were similar between those who received cranberry and placebo capsules (Table 2). Overall daily consumption of capsules and consumption with meals were 51% and 98%, respectively, with no differences between the two groups. The odds of good compliance (i.e., ≥75% of capsule consumption) was not associated with the use of cranberry or placebo capsules (OR, 0.7 [95% CI, 0.2–2.8]; *p*=0.8). More than half of participants reported gastrointestinal intolerance, which was statistically insignificant between the two groups (Table 2).

Compliance data were available for 74% of participants for month 1, 71% for month 2, 67% for month 3, 65% for month 4, 41% for month 5, and 8% for month 6. The monthly compliance rates for cranberry-treated participants were consistently lower by approximately 10%,

TABLE 1. DEMOGRAPHIC CHARACTERISTICS

Variable	Cranberry group (n=24)	Placebo group (n=25)	p-Value
Mean maternal age ± SD (y)	30.9 ± 6.2	31.0 ± 7.1	0.9
Gravida			0.2
0	2 (9)	0	
1	6 (26)	9 (36)	
2	4 (17)	8 (32)	
≥3	11 (48)	8 (32)	
Para			0.8
0	12 (52)	11 (44)	
1	6 (26)	8 (32)	
≥2	5 (22)	6 (24)	
Ethnicity/race			0.09
Hispanic	15 (63)	18 (72)	
White	1 (4)	5 (20)	
Black	4 (17)	1 (4)	
Asian/other	4 (17)	1 (4)	
Enrollment site			0.9
Long Beach Memorial	11 (46)	11 (44)	
University of California, Irvine	13 (54)	14 (56)	
Insurance status			0.5
Government	18 (75)	21 (88)	
Private/other	6 (25)	3 (13)	
Years in school			0.4
0–8	1 (4)	0 (2)	
9–12	12 (52)	16 (67)	
≥13	10 (44)	8 (33)	
Employment	16 (67)	16 (64)	0.8
Prior urinary tract infection ^a	5 (21)	7 (28)	0.7
Routine sex before pregnancy	20 (87)	19 (79)	0.7
Smoker	0	2 (8)	0.5
Alcohol use	0	1 (4)	1.0
Drug use	0	1 (4)	1.0
Comorbid conditions ^b			
Hypertension	0	4 (21)	0.1
Gestational diabetes	1 (6)	2 (11)	1.0
Any infection	0	1 (5)	1.0

Unless otherwise noted, values are expressed as number (percentage) of participants.

^aThere were 7 cases of asymptomatic bacteriuria occurring in 5 participants.

^bData for some participants were unavailable. None of the participants reported hyperthyroid disorder, cardiac conditions, or systemic lupus erythematosus.

SD, standard deviation.

TABLE 2. COMPLIANCE AND TOLERABILITY OVER STUDY PERIOD

Variable	Cranberry group	Placebo group	p-Value
Compliance			
Participants (<i>n</i>)	16	22	–
Mean compliance rate ± SD (%)	77 ± 22	86 ± 11	0.2
Achieved ≥75% compliance ^a	11 (69)	17 (77)	0.7
Consumed capsules daily (%) ^b	33 (51)	50 (51)	1.0
Consumed capsules with meals ^b	63 (97)	97 (98)	0.7
Tolerability			
Participants (<i>n</i>)	17	22	–
Gastrointestinal intolerance ^c	13 (77)	12 (55)	0.2
Nausea	5 (29)	4 (18)	
Constipation	3 (18)	6 (27)	
Vomiting	4 (24)	4 (18)	
Heartburn	4 (24)	2 (9)	
Loss of appetite	3 (18)	3 (14)	
Diarrhea	1 (6)	0	
Stomachache	1 (6)	0	
Taste intolerance	1 (6)	0	0.4

Unless otherwise noted, values are expressed as number (percentage) of participants.

^aCalculated by using capsule count for all follow-up visits over the entire study period.

^bDetermined by patient reporting and based on 165 total events, with 65 in the cranberry capsule group and 99 in the placebo group.

^cA participant may experience multiple symptoms of gastrointestinal intolerance.

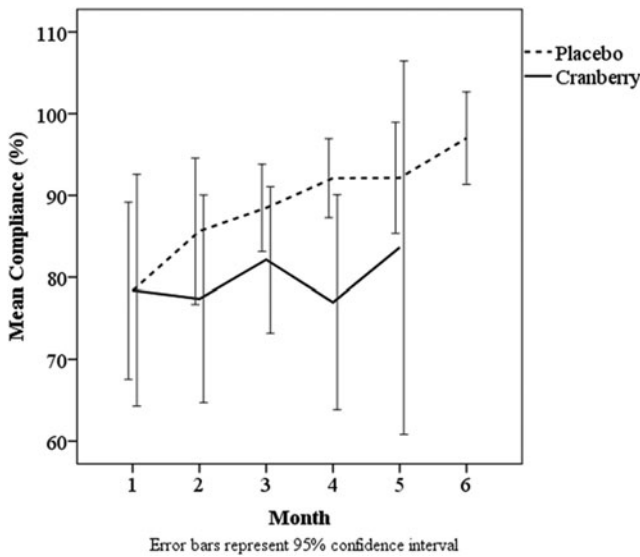


FIG. 2. Mean compliance rate during study period.

albeit not statistically significantly so, than those for the placebo-treated participants from the second month until the end of the treatment period (Fig. 2). Intra-participant compliance varied throughout the treatment period and contributed to 57% variability in the compliance rates (data not shown).

Multivariate logistic regression and linear GEE models (using the exchangeable working correlation matrix structure) showed that treatment group was a significant predictor of achieving 75% or greater compliance. Not accounting for intra-participant correlation, logistic regression showed a significant interaction effect in cranberry treatment over time (OR, 1.78 [95% CI, 1.03–3.09]; $p=0.04$). Similarly, linear GEE analysis, which integrated intra-participant variability, revealed a significant interaction effect with cranberry treatment over time (OR, 1.54 [95% CI, 1.08–2.19]; $p=0.02$). The log-odds ($\geq 75\%$ compliance) was calculated as $0.202 + (0.430 \times \text{number of months}) + (0.405 \text{ if received cranberry}) + (-0.531 \times \text{number of months if received cranberry})$. The corrected full log quasi-likelihood under the independence model criterion for the linear GEE model was 185.

Cranberry consumption, with additive and interaction time effects, was not a significant predictor of compliance rates (as a continuous variable) by using the linear and profile mixed effects and GEE models. Gastrointestinal intolerance, with additive and interaction time effects, was not

TABLE 3. UROPATHOGENS CAUSING ASYMPTOMATIC BACTERIURIA

Pathogen	Cases (n)	Cranberry group (n)	Placebo group (n)
<i>Escherichia coli</i>	4	1	3
<i>Enterococcus</i> group D	1	1	0
<i>Klebsiella pneumoniae</i>	1	0	1
<i>Proteus mirabilis</i>	1	0	1

TABLE 4. OBSTETRIC AND NEONATAL OUTCOMES

Variable	Cranberry group (n=14)	Placebo group (n=19)	p-Value
Male infants	4 (29)	11 (58)	0.09
Mean gestational age at delivery \pm SD (wk)	39.1 ± 1.4	39.2 ± 1.4	0.9
Preterm delivery <37 wk	1 (7)	2 (11)	1.0
Route of delivery			0.4
Vaginal	9 (64)	15 (79)	
Cesarean	5 (36)	4 (21)	
Mean birth weight \pm SD (g)	3407 ± 446	3413 ± 532	1.0
Low birth weight <2500 g	1 (7)	1 (6)	1.0
1-min Apgar score <7	3 (21)	0	0.07
5-min Apgar score <9	2 (14)	0	0.2
Admission to neonatal intensive care unit (%)	2 (14)	1 (6)	0.5

Unless otherwise noted, values are expressed as number (percentage) of participants.

a significant predictor of compliance or study withdrawal by using the linear and profile GEE models.

Seven cases of ASB occurred during the study in 5 participants: 2 of 24 (8%) in the cranberry-treated group and 3 of 25 (12%) in the placebo-treated group (Table 3). The most common uropathogen was *Escherichia coli*. No cases of cystitis or pyelonephritis were seen during this investigation.

Nearly 20% of women dropped out after enrollment and before completion of their first monthly follow-up visit. These women were excluded from the 49 participants who were evaluated in this study. These 49 participants were followed until their infant delivery or withdrawal from the study. Thirty-three participants (67%) remained in the study until delivery. These 33 women completed the first 4 visits: 16 of 27 (59%) from UCIMC and 17 of 22 (77%) from LBMHC. There were 32 patients with 5 visits, 24 patients with 6 visits, and 4 patients with 7 visits, reflecting delivery occurrence over the period of surveillance.

Overall, 30% of participants withdrew for variety of reasons, but only 1 for intolerability (i.e., loss of appetite) to the cranberry capsules. The odds of study withdrawal were not significantly higher with cranberry capsules compared with placebo (OR, 2.3; 95% CI, 0.7–7.7; $p=0.3$). The main reason for study withdrawal was administrative factors, occurring in 9 of 49 (18%) participants (i.e., insurance coverage changes precluded continued medical care in the study facilities). Four of 49 participants (8%) withdrew because of disinterest with therapy over time.

Of the 33 participants who participated until delivery, 14 received cranberry capsules and 19 placebo. None of these participants had antepartum complications, such as fetal malformation, intrauterine fetal growth restriction, oligohydramnios, or polyhydramnios. Neonatal outcomes were similar between the two groups (Table 4).

Discussion

The investigation was intended to provide an alternative approach to the reduction of ASB in pregnancy and its

associated adverse perinatal outcomes with daily cranberry ingestion. Scientific evidence to support the use of cranberry for the prevention and treatment of UTIs is limited by small sample sizes, a lack of focus on reproductive-age women, identification of symptomatic UTIs after daily cranberry juice ingestion, and inadequate assessment of dosing regimens and duration of therapy.¹³ Most important, there are only limited data on the efficacy of daily cranberry ingestion during pregnancy for the prevention of ASB.⁹

The authors' previous experience, while suggesting a potential benefit for this preventive tactic, was fraught with difficulties in selecting the appropriate dosing regimen for daily cranberry ingestion using juice. Administering an equivalent to the cranberry juice in an encapsulated form was thought to be more acceptable to the study participants. Use of capsule formulations suggests improved compliance and efficacy in this investigation. This approach was supported by data from Stothers, who found yearlong compliance rates of 70%–100% with cranberry capsules, along with lower rates with cranberry juice, in a trial evaluating the clinical effectiveness and cost-effectiveness of cranberries for uroprotection.¹⁴ The compliance rate was 82% in this study, with most participants (74%) consuming either cranberry capsules or placebo achieving good compliance. While the main treatment effect was not significant, there was a significant interaction effect with cranberry treatment over time.

The definition of good compliance here—achieving a 75% compliance rate—is somewhat arbitrary. Compliance reflects adherence and persistence in conforming to a treatment regimen and also the duration of treatment.¹⁵ It is arguably difficult to measure in trials such as this, in which biomarkers for cranberry ingestion are lacking. Previous reports describing methodologic and operational approaches to assessing compliance describe composites and ultimately conclude that patients take less medication than prescribed.¹⁵ Optimal measures of adherence to recommended therapy are lacking for cranberry ingestion because there is no biomarker for its consumption readily available at this time.

Approximately 30% of participants could not complete the study to delivery for various reasons, such as insurance restrictions, lack of interest in continuation, and intolerance. Of those who remained within the care catchments, the ability to comply over the long term was much less than anticipated, as evidenced by the limited (only 8%) compliance data at month 6. Ten participants (7 of whom received cranberry capsules) expressed disinterest in continued participation in the trial within the first 4 weeks after enrollment. The participants cited inconvenience with daily capsule ingestion. Only one participant stopped daily capsule ingestion for intolerance.

The 2012 Cochrane review for cranberry for the prevention and treatment of UTI¹³ reported previous evidence that cranberry juice may have decreased the number of symptomatic UTI over a 12-month period for patients with recurring UTIs. However, this review suggests that, from three small studies, there are no statistically significant differences in cranberry products compared with antibiotics for UTI prevention. The subsequent published trials had major limitations, including attrition bias, small sample sizes, and lack of intention-to-treat analysis.¹⁵

The current study has some limitations, including the small sample size and lack of bioassay for compliance. Most participants withdrew as a result of insurance changes. Some non-compliance may be attributed to cultural considerations in the Hispanic community.¹⁶ Common barriers to consistent use of prenatal supplements use among minority women included fear of intake for fetal adverse effects and skepticism toward the efficacy and necessity of prenatal supplements.¹⁶ Intangible or gradual results can prevent patients from taking prophylactic health care measures in general. Greater acceptability and benefit of this approach might be found in persons within different socioeconomic status and broader acceptance of participation in clinical trials. Conclusive information on the benefits of daily cranberry capsule intake can be gleaned only from larger clinical trials in which consistent treatments are applied in compliant patient populations.

Acknowledgments

Financial support was received for this investigation by Ocean Spray Cranberries, LLC, Lakeville-Middleboro, Massachusetts. Theralogix donated the cranberry capsules used for this trial. The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant UL1 TR000153. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author Disclosure Statement

No competing financial interests exist.

References

1. Romero R, Oyarsun E, Mazor M, et al. Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. *Obstet Gynecol* 1989;73:576–582.
2. Kincaid-Smith P, Buller M. Bacteriuria in pregnancy. *Lancet* 1965;1:395–399.
3. McGrady GA, Daling JR, Pterson DR. Maternal urinary tract infection and adverse fetal outcomes. *Am J Epidemiol* 1985;121:377–381.
4. Kass EH. Bacteriuria and pyelonephritis of pregnancy. *Arch Intern Med* 1960;105:194–198.
5. Duff P. Pyelonephritis in pregnancy. *Clin Obstet Gynecol* 1984;27:17–31.
6. Stenqvist K, Dahlen-Nilsson I, Lidin-Janson G, et al. Bacteriuria in pregnancy: frequency and risk of acquisition. *Am J Epidemiol* 1989;129:372–379.
7. Patterson TF, Andriole VT. Detection, significance, and therapy of bacteriuria in pregnancy. Update in the managed health care era. *Infect Dis Clin North Am* 1997;11:593–608.
8. Gilstrap LC 3rd, Ramin SM. Urinary tract infections during pregnancy. *Obstet Gynecol Clin North Am* 2001;28:581–591.
9. Wing DA, Rumney PJ, Preslicka CW, et al. Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy: a randomized, controlled pilot study. *J Urol* 2008; 180:1367–1372.
10. Foo L, Lu Y, Howell AB, et al. A-Type proanthocyanidin trimmers from cranberry that inhibit adherence of

- uropathogenic P-fimbriated *Escherichia coli*. *J Nat Prod* 2000;63:1225–1228.
11. Gupta K, Chou MY, Howell A, et al. Cranberry products inhibit adherence of p-fimbriated *Escherichia coli* to primary cultured bladder and vaginal epithelial cells. *J Urol* 2007;177:2357–2360.
 12. Kimble L, Mathison B, Kaspar K, et al. Development of a fluorometric micoplate antiadhesion assay using uropathogenic *Escherichia coli* and human uroepithelial cells. *J Nat Prod* 2014;77:1102–1110.
 13. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev* 2012;10:CD001321.
 14. Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Can J Urol* 2002;9:1558–1562.
 15. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *International Society for Pharmacoeconomics and Outcomes Research (ISPOR)*. 2007;11:44–47.
 16. Tessema J, Jefferds ME, Cogswell M, et al. Motivators and barriers to prenatal supplement use among minority women in the United States. *J Am Diet Assoc*. 2009;109:102–108.

Address correspondence to:
Deborah A. Wing, MD, MBA
Department of Obstetrics-Gynecology
University of California, Irvine
101 The City Drive South
Building 56, Suite 800
Orange, CA 92868
E-mail: mfm@uci.edu

Copyright of Journal of Alternative & Complementary Medicine is the property of Mary Ann Liebert, Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.