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Evaluation of Syracuse Healthy Start's Program for Abnormal Flora Management to Reduce Preterm Birth Among Pregnant Women

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Abstract

Randomized trials of bacterial vaginosis (BV) treatment among pregnant women to reduce preterm birth have had mixed results. Among non-pregnant women, BV recurs frequently after treatment. Randomized trials of early BV treatment for pregnant women in which recurrence was retreated have shown promise in reducing preterm birth. Syracuse's Healthy Start (SHS) program began in 1997; in 1998 prenatal care providers for pregnant women living in high infant mortality zip codes were encouraged to screen for abnormal vaginal flora at the first prenatal visit. Vaginal swabs were sent to a referral hospital laboratory for Gram staining and interpretation. SHS encouraged providers to treat and rescreen women with bacterial vaginosis or abnormal flora (BV). We abstracted prenatal and hospital charts of live births between January 2000 and March 2002 for maternal conditions and treatments. We merged abstracted data with local electronic data. We evaluated the effect of BV screening before 22 weeks gestation, treatment, and rescreening using a retrospective cohort study design. Among 838 women first screened before 22 weeks, 346 (41%) had normal flora and 492 (59%) women had BV at a mean of 13 weeks gestation; 202 (24%) did not have treatment documented and 290 (35%) received treatment at a mean of 15 weeks gestation; 267 (92%) of those treated were rescreened. Among pregnant women with early BV, 42 (21%) untreated women and 28 (10%) treated women delivered preterm (Odds Ratio [OR] 0.4, 95% confidence interval [CI] 0.2–0.7)). After adjustment for age, race, prior preterm birth and other possible confounders, treatment remained associated with a reduced risk of preterm birth compared to no treatment (aOR = 0.5, 95% CI 0.3–0.9); the aOR for women with normal flora was not significantly different. Conclusion: Screening, treatment, and rescreening for BV/abnormal flora between the first prenatal visit and 22 weeks gestation showed promise in reducing preterm births and deserves further study.

Keywords: Premature birth, Vaginosis-bacterial, Prenatal care

Introduction

Vaginal flora changes characteristic of bacterial vaginosis (BV), such as loss of lactobacilli, are common and frequent [end of pg 1020] among healthy women [1–3]; in one nationally representative study, 29% of women and 25% of pregnant women in the US had BV [2]. Longitudinal studies have shown that most women regain predominance of vaginal lactobacilli without therapy and remain asymptomatic [1]. However, a minority of women retain abnormal flora for periods from weeks to months [3], and some may develop symptoms [4]. Among symptomatic women with BV who receive therapy, recurrences are common; up to one-third of women have a recurrence after1–3 months [5]. Women may benefit from repeated therapy to help maintain normal vaginal lactobacilli [5].

Among pregnant women, vaginal flora changes and BV are also common, regardless of symptoms [2]. While most also regain normal flora over the course of their pregnancy, in some women abnormal flora persists [6]. Most pregnant women with BV or abnormal flora deliver at or near term. However, BV increases the risk of developing several adverse outcomes, including preterm birth [7]. The hypothesized mechanism is ascension of vaginal bacteria into the uterine cavity, provoking infection, inflammation, and premature labor [8]. Vaginal

contents are in communication with the uterus until the fusion of the decidua capsularis with the decidua parietalis at 14–16 weeks of gestation [9]. Therefore, BV treatment has been evaluated as a tool to reduce preterm birth.

Each randomized trial evaluating BV treatment during pregnancy has used a different medication, dose, gestational age at treatment, population, and definition of BV [10], making comparisons and conclusions difficult. Some trials have shown no effect, some increases, and some decreases in preterm birth [10, 11]. In three randomized trials BV treatment was repeated among women who still had abnormal flora after the first treatment [12–14]; preterm birth was 4 and 10%, 5 and 6%, and 26 and 36% in the treatment and placebo groups, respectively. Two trials showed significant reductions in preterm birth. Citing lack of consistent benefit and the possible risk of harm, in 2008 the US. Preventive Services Task Force (USPSTF) recommended against routine screening of pregnant women for BV [10].

We evaluated the effect of early screening (\22 weeks gestation), treatment, and rescreening with retreatment if needed among pregnant women in Syracuse NY. We hypothesized that early treatment of BV or abnormal flora, timed to prevent fetal inflammation or infection and to treat possible ascension of vaginal bacteria into the uterus, with re-treatment for recurrent BV/abnormal flora as needed, would reduce preterm birth. We compared outcomes among (a) screened women who had BV/abnormal flora and were treated, (b) screened women who had BV/ abnormal flora but had no treatment documented and (c) similarly screened women who had normal flora.

Methods

Syracuse Healthy Start Program

The Health Resources and Services Administration (HRSA) funds local Healthy Start programs. Each program is a local effort to reduce infant mortality. New York State's Onondaga County Health Department (county seat: Syracuse) began receiving Healthy Start funding in 1997. The program targeted populations living in the census tracts that had the highest infant mortality rates; these census tracts corresponded to zip codes in inner-city Syracuse (''high risk'' zip codes).

Several programs were initiated for pregnant women and providers caring for women in these high risk zip codes, including promotion of early prenatal care, screening for sexually transmitted diseases, referral to the Women, Infants, and Children nutritional program (WIC), a home visit by a public health nurse, smoking cessation assistance, and early pregnancy screening for bacterial vaginosis and abnormal flora by Gram stain. BV/abnormal flora screening, treatment, and rescreening was started in 1998.

Screening and Treatment for Genitourinary Infections

The Syracuse Healthy Start (SHS) program recommended that obstetric providers caring for women residing in the high risk zip codes test for chlamydia, gonorrhea, and bacteriuria and screen for vaginal flora abnormalities [15] at the women's first prenatal visit. These providers were encouraged to send a swab of vaginal fluid from these women to the main delivery hospital's microbiology laboratory for smear and Gram staining. Laboratory technicians were trained to perform vaginal Gram stains and routine quality control for the interpretation of Gram stain results was established [15]. The Pace 2 (Gen-Probe, Inc., San Diego, California) was used to detect chlamydia and gonorrhea. Within 1 week, results of chlamydia and gonorrhea testing, Gram stain testing, and other routine tests were sent to the provider. Providers were encouraged to treat women [16] whose Gram stain was interpreted as abnormal (i.e., abnormal flora or bacterial vaginosis), to rescreen with Gram stain after 4–6 weeks, and retreat if abnormal flora or BV were present [12–14, 16]. Providers were also encouraged to screen women for abnormal flora regardless of gestational age if preterm labor was suspected and treat women who had BV/abnormal flora [16]. The intent of the program was for screening to occur at the first prenatal visit. However, not all eligible women were screened, some were screened after the enrollment window (e.g.C22 weeks) used in most trials to date, and not all women with BV/abnormal flora had treatment documented. We performed medical [end of pg 1021] chart reviews to evaluate the impact of the screening, treatment, and rescreening among live births born from January 2000 through March 2002. More than 99% of women were screened and treated, if necessary, for chlamydia, gonorrhea, and asymptomatic bacteriuria.

Chart Review

We reviewed prenatal and hospital charts for all women who lived in the high risk zip codes and who delivered a live-born infant at the major delivery hospital during January 2000 through March 2002 (n = 3,109). One abstraction form was generated for each infant. Prenatal charts were reviewed in out-patient settings. If access to prenatal charts from a provider's office was denied, we reviewed the prenatal summary transmitted to the hospital (30% of prenatal charts). Only prenatal care visits that included laboratory screening test results were abstracted. Items abstracted

from the prenatal charts included screening tests performed, symptoms, conditions, treatments, and complications during pregnancy and risk factors for prematurity. In-patient charts were reviewed at the delivery hospital, and items abstracted from the charts included symptoms, conditions, and treatments during delivery hospitalization and perinatal, postnatal, and postpartum outcomes.

Chart reviewers were blind to the purpose of the review and were recruited from the major delivery hospital's obstetrical nursing and paraprofessional clinical staff. Reviewers attended two 3-hour training sessions before reviewing charts independently. The first 10 charts a reviewer abstracted were re-reviewed by one of the authors, who also reviewed 5% of all abstractions. Prenatal chart reviewers were blind to birth outcomes, and in-patient chart reviewers were blind to prenatal conditions. All charts were abstracted onto a Cardiff TeleForm (scannable form) (Cardiff Teleform, Plymouth, Michigan) to facilitate data entry .

Definitions and Outcomes

Gestational age was determined by the first ultrasound performed before 24 weeks gestation. If no such ultrasound was performed (n = 166), gestational age was calculated by using the date of the mother's last menstrual period. If the last menstrual period was not recorded (n = 17), the clinical estimate of gestational age calculated from the birth examination was used. Births that occurred before 37 weeks gestation were defined as premature and births before 28 weeks gestation were defined as extremely premature.

Data Management and Statistical Analysis

Data from the chart reviews were merged with existing electronic databases: the Electronic Birth Certificate, the Regional Perinatal Data System, the SHS enrollment file, and the Onondaga County infant mortality database. We analyzed data using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). We compared the characteristics of the screened women with student's t-test, ANOVA for continuous variables and chi-squared tests for discrete and dichotomous variables, as appropriate. We used bivariate and multivariate logistic regression to evaluate and adjust for possible confounding; we examined the associations of preterm delivery and extremely preterm delivery with the following characteristics: maternal race (white, black, other), maternal and paternal age (\20, 20–29, and [29 years), maternal and paternal education (\high school, high school graduate,[high school), mother's prepregnancy weight (\130 lbs, 130–199 lbs, and[199 lbs), body-mass index (\18.5, 18.5–25, [25), marital status(married, other), gravidity (1, 2–3,[3), prenatal care provider (private, hospital clinic A, community clinic, highrisk clinic, hospital clinic B, other), trimester of onset of prenatal care (1 or 2 [none in 3rd since all included women had onset of prenatal care and their first screening before 22 weeks]), prior preterm birth (yes/no), prior spontaneous abortion (yes/no), smoking status (smoked during pregnancy or not), participation in SHS (yes/no), participation in WIC (yes/no), participation in Aid for Families with Dependent, children (AFDC) (yes/no), domestic violence (yes/no), preterm labor (yes/no), vaginal bleeding (yes/no), diabetes (yes/no), gestational diabetes (yes/no), employment (yes/no), Medicaid (yes/no), living children, and alcohol use (yes/no). Characteristics associated with the outcomes of interest with P\0.15 were entered into a multivariable model and removed in a backwards stepwise manner. Statistical significance was defined as a P\0.05. We used Kaplan–Meier analysis and the log-rank test to test for statistical differences in the gestational ages at delivery between groups.

Results

Study Population and Premature Delivery

Of 3,109 live births, 2,977 (96%) prenatal and 3,070 (99%) inpatient charts were located and abstracted; 2,904 (93%) were successfully matched, and 51 (2%) live-born infant/mother pairs had an inpatient chart only. Of the 2,955 (95%) infant/mother pairs, 2,829 (91%) were singletons/mother pairs. We excluded 781 (28%) women who were not screened for abnormal flora, 1,162 (41%) women whose first screening occurred at or after 22 weeks of gestation, and 48 (2%) women with no or unknown prenatal care, leaving 838 [end pg 1022] (30%) infant/early screened mother pairs for analysis. Compared to the women who were not screened, women who were screened were significantly more likely to be black, younger than 29 years, have a high school education or less, not married, multigravid, smokers, have a previous preterm birth, to attend the community or high-risk clinic for prenatal care, be enrolled in SHS, unemployed, have more living children, and to be on WIC. Compared to women who were screened at 22 weeks or later, women who were screened before 22 weeks were significantly more like to attend the community clinic or the high-risk clinic, to have started prenatal care in the first or second trimesters, and to have experienced vaginal bleeding during pregnancy.

Among the 838 women in the analysis, the mean (±SD) onset of prenatal care was 10 weeks (4.3); 126 (15%) delivered prematurely (the prematurity rate among unscreened women and among women screened between 22 and 36 weeks was 12%). Women who delivered prematurely were significantly more likely to be older than 29,

to have started prenatal care in the 2nd vs. 1st trimester, to have experienced a previous preterm birth, and to attend certain prenatal care providers (Table 1). Characteristics of the women by delivery status are shown in Table 1.

Screening and Treatment of BV/Abnormal Flora

Among the 838 women, the mean (±SD) gestation at first screen was 11.8 weeks (4.8); 68 (8%) were first screened before 6 weeks of gestation, 285 (34%) from 6 weeks to before 10 weeks, 215 (26%) from 10 weeks to before 14 weeks, 158 (19%) from 14 weeks to before 18 weeks, and 112 (13%) from 18 weeks to before 22 weeks. Among these women, 187 (22%) were screened once, 386 (46%) were screened twice, 160 (19%) were screened three times, and 105 (13%) were screened 4 or more times. Results from the first screen indicated that 432 (52%) had normal lactobacilli and 406 (48%) had BV/abnormal flora. Of the 432 women who initially had normal flora, 126 (36%) were screened once, 167 (48%) were screened twice, and 53 (15%) were screened three or more times. Of the 306 who initially had normal flora and were rescreened, 67 (22%) were found to have BV/abnormal flora on a second screen; of the 139 (45%) who had normal flora on the first two screens 72 (24%) were rescreened and 16 (5%) were found to have BV/abnormal flora on the third screen; of the 99 (32%) who had normal flora on the first three screens, 16 (5%) were rescreened and 3 (1%) were found to have BV/ abnormal flora. Compared to women without BV/abnormal flora, women with BV/abnormal flora whether detected at the first screen or a subsequent screen were significantly more likely to be black, less than 30 years old, not married, smokers, have a high school education or less, have more than two children, attend certain prenatal care sites, and to be enrolled in SHS and WIC (data not shown).

Of the 492 (59%) screened women with BV/abnormal flora during pregnancy the mean (±SD) gestational age at the first positive screen was 13 weeks (7.7); 202 (41%) were not treated, 223 (45%) were treated once, 52 (11%) were treated twice, 14 (3%) were treated three times, and one was treated 5 times. The mean (±SD) gestational age at first treatment was 15.2 weeks (8.9); 218 (75%) initiated treatment by 20 weeks. After treatment, 268 (92%) were re-screened.

For the first treatment, 500 mg of metronidazole twice daily for 7 days was prescribed to 170 (59%) pregnant women, 250 mg of metronidazole three times daily for 7 days was prescribed to 56 (19%), 2 gm of metronidazole once was prescribed to 34 (12%), intravaginal metronidazole for 5 days was prescribed to 25 (9%), and intravaginal clindamycin was prescribed to 5 (2%). Among women with BV/abnormal flora, there were no significant differences between treated and untreated women in the following characteristics: race, maternal education, prior preterm birth, marital status, number of prior pregnancies or living children, body-mass index, smoking status, prior spontaneous abortion, prenatal care provider, onset of prenatal care, participation in SHS, maternal employment, participation in WIC, or Medicaid receipt. However, compared to treated women, untreated women were more likely to be older than 29 ($P = 0.003$) and weigh less than 130 lb or more than 199 lb ($P = 0.03$).

Prematurity and Extreme Prematurity by Treatment Status

Compared to women who had BV/abnormal flora and were not treated, women who had BV/abnormal flora and were treated had significantly fewer premature deliveries (28 [10%] vs. 42 [21%], odds ratio [OR] 0.4, 95% confidence interval [CI] 0.2–0.7)) A Kaplan–Meier curve of the proportion of women delivered by gestational age at delivery for each of the screened groups shows that women in the treated group started delivering later in gestation than either of the other groups of women ($P = 0.03$, log-rank test) (Fig. 1). The proportion of premature deliveries among women whose Gram stain showed normal flora did not differ statistically from women who had V/abnormal flora and were treated (Table 2). After adjustment for maternal race, age, pre-pregnancy weight, gravidity, prenatal care provider, trimester of onset of prenatal care, prior preterm birth, and smoking status, treatment of BV/ abnormal flora remained significantly associated with a reduction in the risk of preterm delivery (aOR 0.5, 95% CI 0.3–0.8). After the exclusion from the analysis of the 55 [end of pg 1023]

Table 1 Demographic, health care, social, and reproductive characteristics of women and associations with preterm delivery of singleton infant, Syracuse, NY, 2000–2002

Characteristic	Total $N = 838$	Delivered at 37 weeks or later $N = 711$ (%)	Delivered before 37 weeks $N = 127$ (%)	Odds ratio (95% confidence interval)
Race				
White	275 (33)	228 (83)	47 (17)	1.6 (0.8–3.1)
Black	450 (54)	383 (85)	67 (15)	1.4 (0.7–2.6)
Other	105 (13)	93 (89)	12 (11)	referent
Maternal age				
<20 years	179 (21)	155 (87)	24 (13)	1.1 (0.7–1.9)
20–29 years	472 (56)	415 (88)	57 (12)	referent
>29 years	187 (22)	141 (75)	46 (25)	2.4 (1.5–3.7)
Maternal education level				
<High school	370 (44)	320 (86)	50 (14)	0.9 (0.6–1.5)
High school graduate	281 (34)	241 (86)	40 (14)	referent
>High school	187 (22)	150 (80)	37 (20)	1.5 (0.9–2.4)
Marital status				
Married	178 (21)	146 (82)	32 (18)	referent
Not married	660 (79)	565 (86)	95 (14)	0.8 (0.5–1.2)
Gravidity				
1	192 (23)	170 (89)	22 (11)	0.8 (0.5–1.4)
2–3	319 (38)	274 (86)	45 (14)	Referent
>3	327 (39)	267 (82)	60 (18)	1.4 (0.9–2.1)
Pre-pregnancy weight				
<130 lbs.	236 (28)	197 (83)	39 (17)	1.4 (0.9–2.1)
130–199 lbs.	461 (55)	402 (87)	59 (13)	Referent
>199 lbs.	141 (17)	112 (79)	29 (21)	1.8 (1.1–2.9)
Gestational age at first OB visit (median, IQR)	9 (7, 12)	9 (7, 12)	10 (8, 14)	$P = 0.03$
Smoking at first OB visit				
Yes	322 (38)	265 (82)	57 (18)	1.4 (0.9–2.0)
No	515 (62)	445 (86)	70 (14)	referent
Previous preterm birth				
Yes	123 (17)	84 (68)	39 (32)	3.3 (2.1–5.1)
No	715 (85)	627 (88)	88 (12)	referent
Previous spontaneous abortion				
Yes	231 (28)	189 (82)	42 (18)	1.4 (0.9–2.0)
No	607 (72)	522 (86)	85 (14)	referent
Prenatal care provider				
Private	141 (17)	120 (85)	21 (15)	referent
Hospital clinic A	163 (19)	141 (87)	21 (13)	0.9 (0.4–1.6)
Community clinic	431 (51)	375 (87)	56 (13)	0.9 (0.5–1.5)
High-risk clinic	65 (8)	44 (68)	21 (32)	2.7 (1.4–5.5)
Hospital clinic B	8 (1)	6 (75)	2 (25)	1.9 (0.4–10.1)
Other	31 (4)	25 (81)	6 (19)	1.4 (0.5–3.7)
Onset of prenatal care				
1st trimester	653 (78)	566 (87)	87 (13)	referent
2nd trimester	185 (22)	145 (78)	40 (22)	1.8 (1.2–2.7)
Syracuse Healthy Start participant				
Yes	612 (73)	516 (84)	96 (16)	1.2 (0.8–1.8)
No	226 (27)	195 (86)	31 (14)	referent
Mother employed				
Yes	383 (46)	325 (85)	58 (15)	1.0 (0.7–1.5)
No	453 (54)	385(85)	68 (15)	referent

OB obstetrics/prenatal care, *SD* standard deviation, *IQR* interquartile range

Table 2 Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for preterm birth (<37 weeks gestation) and extremely preterm birth (<28 weeks gestation) by screening and treatment status for bacterial vaginosis (BV)/abnormal flora (Gram stain score 4–10), Syracuse Healthy Start, Syracuse, NY, 2000–2002

Group	Total	Preterm delivery			Extremely preterm delivery		
		Preterm $N = 127$, n (%)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	Extremely preterm $N = 13$, n (%)	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)
Screened, BV/abnormal flora positive, treated	290	28 (10)	0.4 (0.2–0.7)	0.5 (0.3–0.8)[a]	2 (1)	0.2 (0.04–0.9)	0.4 (0.1–1.1)[b]
Screened, BV/abnormal flora negative, remained negative	346	57 (16)	0.8 (0.5–1.2)	0.7 (0.4–1.2)[a]	4 (1)	0.3 (0.1–1.1)	0.7 (0.3–1.2)[b]
Screened, BV/abnormal flora positive, remained untreated	202	42 (21)	Referent	Referent	7 (4)	Referent	Referent

Confounders examined: maternal race (*white*, *black*, other), maternal and paternal age (<20, 20–29, and >29 years), maternal and paternal education (<school, high school graduate, >high school), mother's pre-pregnancy weight (<130 lbs, 130–200 lbs, and >199 lbs), body-mass index (<18.5, 18.5–25 25), marital status (married, other), gravidity (1, 2–3, >3), prenatal care provider (private, hospital clinic A, community clinic, high-risk clinic, hospital clinic B, other), trimester of onset of prenatal care (1 or 2 [none in 3rd since all had onset of prenatal care and screening before 22 weeks]), prior preterm birth (yes/no), prior spontaneous abortion (yes/no), smoking status (smoked during pregnancy or not), participation in Syracuse Healthy Start (yes/no), participation in the Women, Infants, and Children program (WIC) (yes/no), participation in Aid for Families with Dependent, children (AFDC) (yes/no), domestic violence (yes/no), preterm labor (yes/no), vaginal bleeding (yes/no), diabetes (yes/no), gestational diabetes (yes/no), employment (yes/no), Medicaid (yes/no), living children, and alcohol use (yes/no)

[a] Adjusted for maternal race, age, mother's pre-pregnancy weight, gravidity, prenatal care provider, trimester of onset of prenatal care, prior preterm birth, and smoking status

[b] Adjusted for prior preterm birth and mother's employment status

women with BV/abnormal flora whose treatment began after 22 weeks gestation, or of the 52 women who had normal flora before 22 weeks and had BV/abnormal flora detected after 22 weeks, the results were unchanged (data not shown). If the treatment group includes only women who received oral metronidazole for 1 week, results were similar (aOR 0.4, 95% CO 0.2–0.8)—all medications appeared to contribute to the reduction in prematurity except the 2 gm dose of metronidazole (data not shown). There was a reduction among white women (treated 12% vs. untreated 23%, OR 0.5, 95% CI 0.2–1.3) and significant reduction among black women (9% vs. 20%, OR 0.4, 95% CI 0.2–0.8). There was a reduction among women with a previous preterm birth (28% vs. 40%, 0.6 95% CI 0.2–1.6) and a significant reduction among women with no previous preterm birth (7% vs. 17%, OR 0.3, 95% CI 0.2–0.7). Compared to women with BV/abnormal flora who were not treated, women with BV/abnormal flora who were treated also had significantly fewer extremely premature deliveries (2 [1%] vs. 7 [4%], OR 0.2 95% CI 0.04–0.9), although the relationship was no longer significant after adjustment for possible confounders (Table 2). [**end of page 1025**].

Discussion

In this population of 838 pregnant women of inner-city Syracuse, screening for BV/abnormal flora with treatment at a mean of 15 weeks gestation reduced the risk of preterm delivery (10% vs. 21%). All BV and abnormal flora in this population was diagnosed by trained microbiologists in one hospital laboratory using standard Gram stain criteria [15], 226 (78%) of treated women received one of two 7-day oral metronidazole regimens [16], and similar to recent randomized trials [11, 13], gestational age at birth was determined by ultrasound before 24 weeks gestation. There was a notable reduction in preterm birth among black women (9% vs. 20%). This is the first report of BV screening and treatment initiated early during pregnancy in the US. While the intent of the program was to initiate screening and treatment at the first prenatal visit, prenatal care providers varied in their adherence: 781 (28%) of eligible women were not screened, 1,162 (41%) were first screened after 22 weeks gestation, and 290 (59%) of those with BV/abnormal flora were offered treatment. However, among women who were screened, a majority of women were screened more than once, and 92% women who received treatment were rescreened, fulfilling an important aspect of the program.

Compared to unscreened women, the characteristics of screened women put them at higher risk for preterm birth; the preterm birth rate among these women (15%) was higher than among unscreened women (12%), suggesting that the focus of SHS on inner-city Syracuse was merited. Women with BV/abnormal flora in this population had similar characteristics to women with BV in other studies: race, marital status, education, and socioeconomic status were all associated with BV [1, 2]. There were few significant differences between women screened before 22 weeks and those screened later except onset of prenatal care and prenatal care provider, and

except for age and prepregnancy weight, we could not detect significant differences between treated and untreated women. It is unknown whether these results are generalizable to all pregnant women.

The timing of screening and treatment, and rescreening among these women was similar to the timing of screening, treatment and rescreening in a randomized placebocontrolled trial among 409 pregnant British women. In this trial, screening and treatment was initiated at 13–20 weeks gestation and women were rescreened for BV/abnormal flora and retreated for recurrence according to their randomization assignment 20–24 days after their first treatment [12]. Compared to placebo, treated women experienced a significant reduction, similar in magnitude to that in our evaluation, in preterm delivery (4% vs. 10%, P\0.03). A randomized trial in Sweden took a similar approach [13]; 809 women were randomized and initially screened between 10 and 14 weeks, rescreening occurred at 24 and 31 weeks, and treatment was repeated for women with recurrent BV/abnormal flora. While the preterm delivery rate did not significantly differ (5.1% treatment vs. 6.1% placebo), spontaneous births at\33 weeks gestation were significantly lower in the intervention group (0.3% vs. 1.3%, OR 0.14, 95% CI 0.02–0.95). In our analysis, women who were treated also had fewer deliveries at\33 weeks compared to women who were not treated (data not shown). Both of these randomized trials used intravaginal clindamycin, whereas the majority of women in our study were prescribed an oral metronidazole regimen for their first course of therapy. However, all of these regimens have similar efficacy for treatment of BV [16]. A third randomized trial in the USA among high risk pregnant women (previous preterm birth or pre-pregnancy weight of \130 lb) initiated screening and treatment of BV with oral metronidazole and erythromycin at 23 weeks and retreated women with recurrent BV at 25–29 weeks [14]. In the subanalysis of women with BV, high risk women also had a reduced rate of preterm delivery (31% vs. 49%, $P = 0.006$).

Biologic reasons may explain why the timing of treatment and retreatment are important. The characteristics of the fetal inflammatory response syndrome have been described [8, 17, 18]; an infected or inflamed fetus stimulates labor and delivery through the release of cytokines and proteolytic enzymes. A fetus may also suffer increased morbidity, such as cerebral palsy and bronchopulmonary dysplasia, from an intraamniotic inflammation that precedes fetal inflammation [8]. However, a fetus is not capable of generating such an inflammatory response until it has developed some functionality to its immune system, which generally occurs between 15 and 19 weeks of gestation [19]. Multiple studies have shown that once the inflammation/infection has reached the amniotic cavity and labor is stimulated, it is difficult to stop [17]. Therefore, prevention of this cascade before it has started may be critical.

Vaginal bacteria can ascend into the uterus and establish a nidus of infection until the fusion of the decidua capsularis with the decidua parietalis at 14–16 weeks of gestation; this fusion in effect seals the uterus from vaginal contents [9]. The timing of the fusion and the nascent fetal inflammatory response could explain why BV early in pregnancy is associated with late miscarriage [20] and very preterm birth [7, 20], why BV detected only in the latter half of pregnancy has a smaller or little effect [21] (the route of ascension is closed) and why late treatment may have no effect (those susceptible have already delivered). Therefore, maintenance of normal flora, e.g. treatment and retreatment if needed, of abnormal flora, until after the [**end of page 1026**] fusion of the decidua, to prevent the development of intraamniotic infection and an inflammatory response in the fetus, may prevent preterm, particularly early preterm delivery, as seen in this evaluation and other studies [12, 13]. Subgroups of women with BV/abnormal flora may be more likely to develop complications, and genetic factors may be involved, because only a minority of women with BV/abnormal flora early in pregnancy miscarry or deliver prematurely.

There are important limitations to this analysis. Most importantly, treatment was not randomized; therefore, the results could entirely reflect the effect of unknown or unmeasured confounders [22]. The effect of unmeasured confounders is demonstrated in Fig. 1; women with abnormal flora who were treated had longer gestations than women who had normal flora. A second limitation is that prenatal care providers played a critical role in determining who was screened and treated; this may also explain the effect we found. We cannot explain why certain women were treated and others were not; anecdotally some providers were enthusiastic about screening and treatment and others were not; some may have selected whom to treat. We could not distinguish a difference in treatment rates between clinics. Third, misclassification bias may have played a role: some women might have been treated, but the treatment was not recorded in the chart or found during chart abstraction. Fourth, women might not have taken their medication as prescribed. These possible misclassification biases would have decreased the estimate of the effect for the treatment of abnormal flora. Other possible misclassifications may have occurred based on incorrect chart abstraction, such as in maternal education, weight, and prenatal care provider.

Despite a difference in the drugs used, two randomized trials [12, 13] and our evaluation suggest that an abnormal flora screening intervention starting before fusion of the decidua, taking into account the high recurrence rate of bacterial vaginosis after treatment, for average risk pregnant women may have merit and deserves further study to reduce preterm birth.

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