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Review Article

Association of Bacterial Vaginosis and Time to Conception & Infertility: A Prospective Cohort Study

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Abstract

Objective: To evaluate the association of Bacterial Vaginosis (BV) with times to conception and infertility in a cohort of women who have discontinued their method of contraception in an attempt to conceive.

Materials and methods: The Fertility after Contraceptive Termination (FACT) Study is a prospective cohort study of women discontinuing their method of contraception to attempt conception. We grouped participants into two categories based on the presence of BV at baseline exam: BV-positive (Nugent score>7) and BV- negative (Nugent score<7). We calculated median times to conception by BV status and used a stratified Cox proportional hazards model to control for potential confounding variables.

Results: Of our cohort of 314 participants with Gram stain data at baseline and time to conception data, 28% (87/314) of participants were diagnosed with BV, and 227 participants (72%) were negative. BV was positivity associated with younger age, black race, higher body mass index, lower socioeconomic status, gravidity, and smoking status. The median time to conception in the BV-positive group was 6.4 months compared to 5.5 months in the negative group. BV positivity was not associated with time to conception in a Kaplan-Meier survival analysis (P=0.82), and this remained unchanged in adjusted analysis controlling for confounding variables stratified by race. The 12-month infertility rate after discontinuing contraceptive methods was 27.0% in the BV-negative group and 28.8% in the positive group.

Conclusion: In our cohort, baseline BV positivity was not associated with longer times to conception or infertility.

Introduction

In the U.S., about 1 in 5 (19%) heterosexual women aged 15 to 49 years with no prior births are unable to get pregnant after one year of trying (infertility) [1]. Although many factors contribute to the diagnosis of infertility (failure to get pregnant within 1 year), one recognized preventable risk factor for infertility is genital tract infections [1]. Untreated lower genital tract infections may eventually lead to ascending infections such as pelvic inflammatory disease (PID) [2]. PID involves inflammation and infection of the upper genital tract and may cause structural or functional fallopian tube damage known as tubal factor infertility [2,3]. Tubal factor infertility is estimated to affect as many as 20% to 25% of women who are diagnosed with infertility.

The vaginal ecosystem is highly complex. Lactobacilli are the predominant species in the vaginal microbiota of most women [4-6]. Lactobacilli protect against colonization of pathogenic bacteria by producing antimicrobial biproductions and lactic acid as well as low-level immune system activation [6]. The disruption in the normal vaginal ecosystem changes the microflora of the healthy vagina. This disruption alters the pH and predisposes to reproductive tract infections and Sexually Transmitted Infections (STIs) which can result in infertility [7]. Bacterial Vaginosis (BV) is an anaerobic overgrowth characterized by an absence of lactobacilli species and an abundance of anaerobes. The following bacteria are commonly associated with BV: *Gardnerella vaginalis, Atopobium vaginae, Megasphaera spp., Dialister spp., Mobiluncus spp., Sneathia amnii, Sneathia sanguinegens, Porphyromonas spp.,* and *Provotella spp* [7,8]. Bacterial Vaginosis (BV) is considered as a risk factor for Sexually Transmitted Infection (STIs) and potential ascending spread to the upper genital tract (endometritis, salpingitis, and oophoritis) and resultant tubal factor infertility [6]. Given that vaginal BV may be the initial insult to predispose women to infection, it is important to evaluate the association between BV and time to conception and infertility.

In our search of the medical literature, we did not find a contemporary prospective study that evaluates the association of BV and subsequent fertility rates. The aim of this analysis was to evaluate the association of BV and time to conception and infertility in a cohort of women discontinuing their method of contraception in an attempt to conceive. We hypothesized that women with BV will have longer times to conception and are less likely to conceive within 12 months than women without BV.

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Methods

The FACT (Fertility after Contraceptive Termination) Study is a multicenter, prospective cohort study of more than 425 participants who discontinued their method of contraception to attempt conception. Participants discontinuing Oral Contraceptive Pills (OCPs), condoms, transdermal contraceptive patch, contraceptive vaginal ring, subdermal etonogestrel implant, Depot Medroxyprogesterone Acetate (DMPA), or the copper or hormonal Intrauterine Device (IUD) were eligible to participate. In addition, FACT study participants met the following inclusion criteria: 1) 18-35 years of age; 2) sexually active with a male partner; 3) ability to consent in English or Spanish; and 4) willing to comply with all study procedures and follow-up. We excluded patients who: 1) had a positive pregnancy test; 2) had a history of infertility; 3) were surgically sterile; and 4) used Depot Medroxyprogesterone Acetate (DMPA) in the 5 months prior to trying to conceive, as DMPA can be associated with a longer return to fertility [9]. We obtained institutional review board approval prior to participant recruitment, and all participants signed an informed consent form.

Potential participants were identified from OB/GYN and family planning clinics in the following regions: Aurora, Colorado; Indianapolis, Indiana; Los Angeles, CA; Philadelphia, Pennsylvania; Salt Lake City, Utah; and St. Louis, Missouri. Following enrollment, a research assistant administered a survey including questions regarding demographic and reproductive characteristics, medical/surgical history, date of contraceptive method discontinuation; date participants began trying to conceive, partner's reproductive history, and frequency and timing of intercourse.

Upon enrollment, vaginal swabs were collected for sexually transmitted disease testing, and a wet mount was performed by a clinician, and a dried slide was put aside for Gram Stain. Vaginal swabs were obtained for nucleic acid amplification testing for the following current Sexually Transmitted Infections (STI): *Chlamydia trachomatis, Neisseria gonorrhea, Mycoplasma genitalium*, or *Trichomonas vaginalis*. Serum was collected to analyze serology for evidence of past *C. trachomatis, M. genitalium*, or *T. vaginalis* infection.

The Gram stain is the gold-standard for the diagnosis of BV and has been used in laboratories since 1965. Gram stains are more specific for BV with high interobserver and intraobserver reproducibility than Amsel's criteria [10]. A standardized scoring system for the diagnosis of BV, the Nugent score, is most often used in research studies to evaluate for BV. With the Nugent score, the slide is examined for the quantity of Gram-positive rods and lactobacilli (i.e., normal flora) and Gram-negative or Gram-variable morphotypes (BV flora) [11]. The results are given as a score of 0 to 3 (normal flora), 4 to 6 (intermediate or mixed flora), and 7 to 10 (BV). We analyzed data from participants who had a Gram Stain and Nugent scoring performed at baseline with 12-months of follow-up data or conceived within the first 12 months. BV slides were sent to Magee-Women's Hospital in Pittsburgh, Pennsylvania for Gram Stain and interpretation using Nugent scoring. We grouped participants into two categories: BV-positive (Nugent score > 7) and BV-negative (Nugent score < 7).

Follow-up surveys were conducted *via* phone at 6, 12, 18, and 24 months after method discontinuation to assess for pregnancy. Follow-up surveys aske/0258d participants about any pregnancies and their pregnancy outcomes that occurred in the past 6 months. We also asked for the frequency and timing of intercourse, menstrual cycle regularity, and any changes to health or medications that may affect fertility. Medical record request authorization forms were sent to all participants so that we could perform medical chart reviews to validate pregnancy outcomes.

We summarized patient demographics and characteristics using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. We compared these variables between BV positive and BV negative group using t-tests, or chi-square test or Fisher exact test when appropriate. Our primary outcomes were time to conception and infertility. The primary exposure of this analysis is a Gram Stain score indicating BV (positive or negative) at baseline. Time to conception was defined as the time from the date of stopping contraceptive method to the date of conception, censoring those who had not yet conceived on the date of last follow up. For women who had reported pregnancy but no record of date of conception or date of last menstrual period, left and interval censoring were used on the basis of follow up interview dates. The Kaplan-Meier survival function was used for the estimates of the fertility rates and the median time to conception and 95% Confidence Intervals (CIs) was estimated. Confounding was defined as a greater than 10% change in the effect size of the BV status on time to conception when the covariate of interest included in the model compared to that without the covariate. Multivariable Cox proportional hazard analysis was conducted stratified by race since race and BV positivity are highly correlated. A Kaplan-Meier Survival Estimate Curve was utilized to estimate time to conception. Stata 14 was used for all the analyses, and all the tests were 2-sided with significant level of 0.05.

Results

From our total cohort, 314 participants met inclusion/exclusion criteria. The demographics and characteristics of the patient population, stratified by BV status, are shown in Table 1. The mean age of the cohort was 28.6 years. The majority were white and non-Hispanic. The body mass index (BMI) of the cohort was distributed between normal (46%), overweight (23%), and obese categories (32%).

Of the 314 participants, 87 (28%) had bacterial vaginosis based on the Nugent score and 227 (72%) did not have BV (See Table 1). Participants with and without a diagnosis of bacterial vaginosis differed in several respects. Bacterial vaginosis was positivity associated with younger age, black race, higher body mass index, lower socioeconomic status, gravida and current smoker.

The median time to conception in the BV-positive group was 6.4 months compared to 5.5 months in the BV-negative group (See Table 2). The 12-month infertility rate after discontinuing contraceptive methods did not differ significantly by BV status. The 12-month infertility rate was 27.0% (95% confidence interval (CI): 21% - 33%) among participants without BV and 28.8% (95% CI: 19% - 38%) among those with BV. The univariable Cox modeling of BV status and other patient characteristics on fertility was shown in Table 3. The time to conception in patients with BV is not statistically significantly different compared to patients without BV, HR=1.03, 95% CI 0.78-1.38. This remained unchanged in adjusted analysis controlling for confounding variables. Our multivariable analysis stratified by race (Black v. non-Black) failed to demonstrate a statistically significant difference in the association of BV positivity and time to conception (See Table 4). The Kaplan Meier survival curves demonstrated no difference in time to conception (See Figure 1; P=0.82).

Table 1: Demographic, reproductive, and sexual characteristics of participants stratified by BV status.

	Overall (N=314)		BV Negative (N=227)		BV Positive (N=87)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Age, mean, SD	28.6	3.8	29	3.5	27.5	4.3	0.001
	N	%	N	%	N	%	
Race							<0.001
White	182	58.7	164	72.9	18	21.2	
Black	100	32.3	43	19.1	57	67.1	
Others	28	9	18	8	10	11.8	
Hispanic							0.369
No	289	92	207	91.2	82	94.3	
Yes	25	8	20	8.8	5	5.7	
BMI							<0.001
<25	142	45.5	117	51.8	25	29.1	
25-30	71	22.8	53	23.5	18	20.9	
>=30	99	31.7	56	24.8	43	50	
SES Low							<0.001
No	224	71.3	188	82.8	36	41.4	
Yes	90	28.7	39	17.2	51	58.6	
Nulligravid							<0.001
No	181	58.2	110	49.1	71	81.6	
Yes	130	41.8	114	50.9	16	18.4	
Current smoker							0.001
No	278	88.8	209	92.5	69	79.3	
Yes	35	11.2	17	7.5	18	20.7	
Current alcohol use							0.073
No	72	23	46	20.4	26	29.9	
Yes	241	77	180	79.6	61	70.1	
Menstrual regularity							0.449
No	35	15.4	23	14.2	12	18.2	
Yes	193	84.6	139	85.8	54	81.8	
Contraceptive method used prior to trying to conceive							<0.001
IUD	163	51.9	118	52	45	51.7	
Implant	49	15.6	21	9.3	28	32.2	
Pills, Patch, or Ring	75	23.9	68	30	7	8	
DMPA	5	1.6	2	0.9	3	3.4	
Others	22	7	18	7.9	4	4.6	
Weekly frequency of intercourse, mean, SD	3.4	3	3.1	2.7	4.2	3.6	0.008
Weekly frequency of intercourse, category							0.004
<=2	122	39.1	100	44.1	22	25.9	
>2 and <=4	128	41	90	39.6	38	44.7	
>4	62	19.9	37	16.3	25	29.4	

NOTE: BV: Bacterial Vaginosis; SES: Socioeconomic Status; BMI: Body Mass Index; IUD: Intrauterine Device; DMPA: Depot Medroxyprogesterone Acetate

Table 2: Twelve-month conception rates and median times to conception.

	1-year Fertility Rate	95% Confidence Interval		Median time to conception (months)	95% Confidence Interval	
BV Positive	71.2	61.6	80.8	6.4	4.1	7.6
BV Negative	73	67.1	78.8	5.5	4.4	6.7
BLACK	55.2	47.8	62.6	8.8	6.5	14.8
WHITE	77.3	71.9	82.6	5.3	4	6.2
OTHER	73.8	59.6	88	4.7	2.4	8.3

Note: BV: Bacterial Vaginosis

Table 3: Univariable modeling of effects of patient characteristics on fertility.

Characteristic variables	HR	95% CI		p-value
BV				
Negative				
Positive	1	0.8	1.4	0.816
Age	1	1	1	0.433
BMI				
BMI<25	Reference			
BMI 25-30	0.8	0.6	1.1	0.151
BMI>=30	0.7	0.6	0.9	0.006
Race				
Black	0.6	0.5	0.8	<0.001
White	Reference			
Others	1.1	0.7	1.6	0.64
Hispanic				
No	Reference			
Yes	1.8	1.3	2.5	0.001
SES Low				
No	Reference			
Yes	0.7	0.5	0.8	<0.001
Nulligravid				
No	Reference			
Yes	1	0.8	1.3	0.76
Current smoker				
No	Reference			
Yes	0.7	0.5	1	0.038
Current alcohol use				
No	Reference			
Yes	1.2	0.9	1.5	0.189
Menstrual regularity				
No	0.7	0.5	1	0.071
Yes	Reference			
Contraceptive method used prior to trying to conceive				
IUD	1.3	1	1.7	0.08
Implant	1.1	0.8	1.6	0.547
PPR	Reference			
Depo	0.7	0.2	2.5	0.554
Others	1.3	0.9	2.1	0.205
weekly frequency of intercourse	1	1	1.1	0.726

NOTE: BV: Bacterial Vaginosis; SES: Socioeconomic Status; BMI: Body Mass Index; IUD: Intrauterine Device; DMPA: Depot Medroxyprogesterone Acetate

Table 4: Multivariable modeling of effects of patient characteristics on fertility stratified by race.

	Among Black Participants				**Among non-Black Participants**			
Characteristic variables	HR	95% CI		p-value	HR	95% CI		p-value
BV								
Negative								
Positive	1.6	1	2.71	0.06	1.33	0.85	2.1	0.207
Age	1	1	1.11	0.213	0.96	0.91	1	0.075
BMI								
BMI<25	Reference							
BMI 25-30	0.8	0.4	1.58	0.482	0.83	0.58	1.2	0.319
BMI>=30	0.8	0.5	1.44	0.471	0.85	0.54	1.4	0.497
SES Low								
No	Reference							
Yes	0.7	0.4	1.28	0.282	1.12	0.61	2	0.719
Current smoker								
No	Reference							
Yes	1.3	0.6	2.9	0.458	0.7	0.36	1.3	0.271

Note: BV: Bacterial Vaginosis; BMI: Body Mass Index; SES: Socioeconomic Status; HR: Hazard Ratio

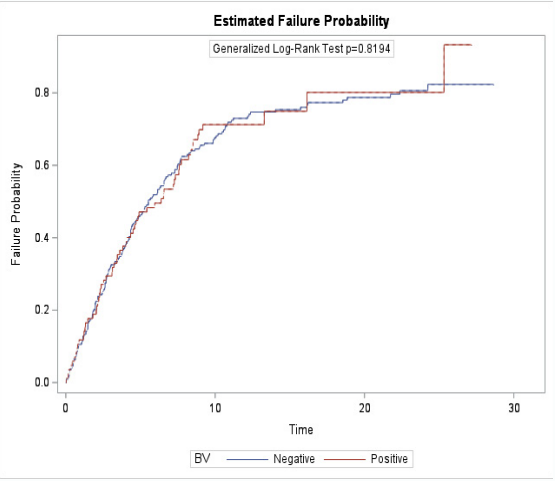

Figure 1: Kaplan-Meier curves – Time to conception (months since stopping contraception).

Discussion

We found no difference in fertility rates and minimal difference (0.9 months) in median time to conception between participants with and without BV. The rates of infertility (failure to conceive within one year) were higher than that reported in the literature, but these rates did not vary based on BV status. While our cohort was selected for the desire to conceive, the group had a number of risk factors that might elevate their infertility rates (i.e., diverse racial/ethnic status, high prevalence of past STIs, etc.).

Several reports in the literature have shown that BV is associated with infertility. The evidence has mostly been directed towards BV being an initial insult towards infection and infertility. In a cross-sectional study evaluating the vaginal flora among healthy women and women with infertility, Babu et al. noted that women with infertility had a higher prevalence of asymptomatic BV compared to healthy women (28% *vs.* 7%) [12]. In a cohort study, Salah et al. also observed a higher prevalence of BV in infertile patients (46%) compared to family planning/fertile women (15%). In addition, they observed that the cumulative pregnancy rate was significantly higher in the patients with BV and unexplained infertility who were treated for BV compared to patients who were not treated. Their regression model showed that BV was one of the significant factors interfering with pregnancy [13]. In a study of 178 women with tubal factor infertility, Durugbo et al. found a 28% prevalence of BV compared to 8% in fertile women (P<0.001) [14]. It is unfortunate that many of these studies demonstrating a positive association of BV and infertility were cross-sectional and failed to control for important confounding variables.

Other studies have refuted the association of BV with subsequent infertility. Gaudoin et al. performed a cross sectional study of women undergoing In-Vitro Fertilization (IVF). These investigators found that women who had BV achieve pregnancy rates with IVF treatments similar to those of women who had no evidence of such infections [15]. Similarly, a meta-analysis of conception rates in infertility patients could not confirm a statistically significant association between BV and conception rates [16].

Our findings further add to the body of scientific literature evaluating the association of BV and conception rates or time to conception. Our study has several strengths including a geographically diverse sample of participants, a reasonably large sample size, and objective assessment of BV by Gram stain. Our multicenter study was the only contemporary prospective cohort study to evaluate the association of BV and time to conception and infertility while controlling for important confounding variables. In addition, we had excellent follow up (>80%). However, our study does have some limitations. Participants may not have accurately recalled the precise ate they stopped their method and started to attempt conception. BV was additionally only sampled at the initial baseline visit, a single point in time. BV status can fluctuate, and vaginal flora can change over time [17]. Our negative findings may be due to a type II error. Based on an estimated 30% prevalence of BV, an infertility rate in the control group of 25%, and a relative risk of infertility in the BV-positive group of 1.5, we needed 162 participants with BV (total sample N=540) to achieve 80% power.

In conclusion, we found no evidence to support the association of BV and prolonged time to conception and infertility. Future studies should assess the vaginal microbiome in the large samples of women to further evaluate vaginal flora and changes over time as potential risk factors and causes of infertility.

Conflict of interest

Dr. Peipert receives research support from CooperSurgical, Merck, and Bayer.

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