Local Interleukin-1beta in Pregnant Women with Bacterial Vaginosis and Adverse Pregnancy Outcomes

Abstract

Objective: To assess if vaginal interleukin-(IL)-1beta in early pregnancy is associated with adverse outcome among BV-positive women.

Study Design: 1,806 women were enrolled at <20 weeks' gestation. 800 women were BV-positive (Nugent 7-10), 707 of them had birth outcome data. Vaginal IL-1beta concentrations were measured in 105 BV-positive women who had an adverse preterm outcome, including 66 preterm births (20-<37 weeks, of which 52 were spontaneous) and 14 late miscarriages (12-<20 weeks), and in 295 BV controls (term normal birth weight infants). The upper (>66th percentile) and lower (<33rd percentile) tertiles of IL-1beta concentrations were compared with the middle tertile (33rd to 66th percentile).

Results: None of the IL-1beta tertiles was associated with increased risk for any adverse preterm outcome, nor preterm birth and miscarriage with or without exclusion of women with concurrent STDs.

Conclusion: IL-1beta is not a risk marker for preterm birth among BV-positive women in early gestation.

Keywords: Vaginal IL-1; Innate immunity; Bacterial vaginosis; Preterm birth; Miscarriage; Adverse pregnancy outcome

Research Article

Volume 5 Issue 4 - 2016

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Received: October 27, 2016 | **Published:** November 08, 2016

Introduction

The availability of biomarkers early in gestation to predict women at elevated risk of adverse pregnancy outcomes is increasingly appreciated as a necessary pre-requisite for future intervention trials to finally reduce the rate of preterm birth (<37 weeks' gestation) [1-6]. Preterm birth (PTB) continues to be a major public health problem with approximately 12% of all US pregnancies ending before 37 weeks' gestation [7]. Recent WHO data estimate a world PTB rate of 9.6% [8]. Approximately 13 million babies are born preterm annually, of which, approximately 500 thousands in North America and 900 thousands in Latin America and the Caribbean [8]. PTB is the main single cause of acute infant morbidity and long-term impairment [8,9]. Early spontaneous preterm deliveries that occur before the 32nd week of gestation, have been strongly associated to intrauterine infection, likely ascending from the vagina, and represent the largest portion of neonatal deaths and neurological problems [7,10]. Bacterial vaginosis (BV) is an altered vaginal flora condition, where the normal lactobacilli flora is substituted with a mixed and variable flora of microaerophilic and anaerobic microorganisms [11]. Although BV is a lower vaginal tract microbial disorder, several investigations have shown that it is associated with PTB generally, early PTB, early and late miscarriage, low birth weight (LBW, <2500 g), and maternal complications [5,7,9,12-16]. However, it is to note that more than 70% of women with BV do not have an adverse birth outcome, thereby, BV is a biomarker with low specificity [12,17,18]. PTB is recognized as a multifactorial disorder, with infection-related effects accounting for the majority of early events [19]. BV is an attractive target for interventions as it is potentially treatable. Numerous randomized clinical trials of antibiotic therapy to reduce PTB have been conducted in pregnant women selected on the basis of various risk factors [7,20-23]. However, so far, the treatment results have been variable including harmful [9,24]. Thus, there is a clear need for biomarkers to better select high risk subgroups of women with abnormal vaginal flora, preferably in early gestation [2,4,7,15,25-28].

BV is a microbial/mucosal immunity disorder [1,3,15,26,27,29-33]. Accumulating evidence suggests that microbes associated with BV modulate the immune response [27,31,33-36]. Many authors have found elevate levels of interleukin (IL)-1alpha or beta in vaginal secretions of BV-positive women compared to healthy controls [34,37-40]. IL-1beta is a member of the IL-1 family, which includes the classical IL-1alpha (IL-1F1) and IL-1beta (IL-1F2) cytokines, IL-1 receptor antagonist (IL-1ra, or IL-1F3), IL-18 (IL-1F4), and the newly described IL-1F5-11 [41]. IL-1alpha is mainly intracellular, whereas IL-1beta can be secreted outside cells in the extracellular fluids, thus it is commonly found in serum and secretions. IL-1beta plays a prominent role in the regulation of the inflammatory response [41]. IL-1beta is able to induce the secretion of several inflammatory factors, such as IL-6, IL-8, tumor necrosis factor-alpha (TNF-alpha), matrix metalloproteinases (MMPs) by many different cell types including vaginal epithelial cells, macrophages, neutrophils, peripheral blood mononuclear cells (PBMC), fibroblasts, endothelial and muscle cells [42,43]. The expression of cytokines such as IL-1beta, IL-6, IL-8, and TNF-alpha by either the fetal or maternal tissues has been demonstrated

to upregulate the activity of a number of uterine and cervical factors (e.g., prostaglandin hormones and their receptors, MMPs, vascular endothelial growth factor and elafin) and leukocytes leading to premature initiation of the parturition process [42-44]. The crucial role of IL-1beta was recently highlighted by a study aimed to determine the relative contributions of individual proinflammatory cytokines and chemokines to the triggering of preterm labor. This investigation showed that in pregnant rhesus monkeys who received intraamniotic infusions of IL-1beta, TNF-alpha, IL-6, IL-8 and saline control, IL-1beta stimulated the most intense contraction patterns, resulting in preterm labor in all cases [43].

Although inflammation is an essential mechanism in response to challenges including microbiological insult and tissue injury, inappropriate or excessive induction of the inflammatory response is itself a well-characterized cause of morbidity and mortality in several pathologic conditions. On the other hand, inflammation is a protective response, thus also a reduced or depressed response could be detrimental predisposing to overwhelming infection [15].

The purpose of this research was to discover specific biomarkers associated with BV able to predict the risk of preterm birth, with special focus on early adverse events. We aimed to assess whether specific levels of vaginal IL-1beta in pregnant women with BV are associated with adverse pregnancy outcome. Specifically, this study assesses if the risk of adverse outcome has a U-shape profile according to IL-1beta levels, based on the hypothesis that both hyper-responders and hypo-responders may constitute subgroups of high risk [15,26,27]. Thus, the upper (>66th percentile) and lower (<33rd percentile) tertiles of IL-1beta concentrations were compared with the middle tertile (33rd to 66th percentile). Our final goal is to find a biomarker to personalize treatment intensity in pregnant women with BV.

Materials and Methods

Study design

The primary aim of this study was to ascertain if a subset of truly at risk BV positive women could be identified via vaginal biomarkers in early pregnancy. The study employed a prospective design where all women enrolling for prenatal care prior to 20 weeks of gestation were asked to participate. For those meeting eligibility criteria and providing written informed consent, vaginal secretions were obtained for diagnosis of BV and banking until birth outcome was determined. Vaginal secretions were analyzed from all BV positive women delivering prior to term and a randomly selected sample of controls among BV positive women delivering term, normal birth weight infants (≥37 weeks' gestation and ≥2500 g). All women attending their first prenatal visit at three hospital-based clinics located in Philadelphia (PA) between January 2002 and September 2004 were screened for eligibility.

Women were considered eligible for participation if they:

a) Were less than 20 weeks pregnant at the time of enrollment,

b) Spoke either English or Spanish,

c) Had a singleton intrauterine pregnancy,

d) Were not HIV positive,

e) Did not seek a therapeutic abortion,

f) Were 18 years of age or older,

g) Underwent a routine pelvic examination at the enrollment visit, and

h) Had no vaginal bleeding at the time of sample collection.

We did not exclude women reporting recent vaginal intercourse based upon our own preliminary work [45]. In an analysis of vaginal secretions obtained from 300 BV positive women from this cohort, IL-1beta concentrations were not correlated with prostate-specific antigen (PSA), which is considered the best marker of seminal fluid contamination of vaginal samples. Furthermore, we did not exclude women that entered prenatal care taking antibiotics or women prescribed antibiotics at the time of their first prenatal care visit. We based this decision upon the fact that women (n = 199) who were taking antibiotics or who were prescribed antibiotics (including penicillin, ampicillin, amoxicillin, aminoglycosides, clindamycin, metronidazole, macrolides, cephalosporins, and others) did not have a different distribution of preterm birth outcomes compared to those women that did not take antibiotics.

Collection of medical data and specimens

At the time of enrollment, seven dacron swabs were used to collect vaginal secretions from the posterior wall of the vaginal fornix and processed as described elsewhere [33]. Vaginal samples were stored frozen in liquid nitrogen soon after collection and shipped on dry ice to a core laboratory, where all measurements were performed. Gram stained smears from all women who were eligible and consented to participate (n = 1,806) were evaluated according to the Nugent score [33,46], by personnel blinded to all other data. BV was defined as a Nugent score of 7-10 [33,46]. The BV diagnosis was not disclosed to the women or their care providers. Only BV positive women were further examined. Pregnancy outcome and gestational age was ascertained after delivery by medical record review. Records were also abstracted to determine whether early births were spontaneous or medically indicated [47]. To ensure accuracy of the information, all medical records were abstracted by trained personnel and all controversial aspects of the chart were flagged and reviewed by three consulting physicians. Sociodemographic, health behavioral and previous medical history, was collected in face-to-face interviews by trained study staff. Body mass index (BMI) was calculated from self reported height and weight information. BMI was defined as weight in kilograms divided by the square of height in meters.

Definitions of outcome

Estimates of gestational age were based on the first ultrasound for most 94.3%, (n = 377) of the 400 study participants in the final analytic sample. For those without an ultrasound (n = 23; 5.75%), gestational age was determined from medical record abstractions. Among all BV positive women, pregnancies that ended in live birth, stillbirth or miscarriage were classified as follows: PTB (live birth

between 20 and <37 weeks of gestation), stillbirth (between 20 and <37 weeks), late miscarriages (between 12 and <20 weeks); early miscarriages (<12 weeks). Adverse pregnancy outcome groups were compared to term, normal birth weight deliveries. Out of the 109 adverse preterm outcomes, 105 had IL-1beta measured. 52 women had spontaneous preterm births (SPTB) of which 19 were early SPTB (between 20 and <34 weeks' gestation) and 33 were late SPTB (between 34 and <37 weeks' gestation). The remaining adverse outcomes were as follows; 17 early miscarriages, 14 late miscarriages, 12 medically induced preterm births, 2 preterm births with no information about induction (not further examined in detail), and 8 stillbirths. Unadjusted comparisons between the term normal weight infants, all adverse preterm outcomes and the six discrete subsets were performed on all three tertiles of IL-1beta, specifically, first (<33rd percentile), second (33rd to 66th percentile), and third (>66th percentile) tertile of IL-1beta concentrations.

Evaluation of IL-1beta concentration: IL-1beta concentration was determined in duplicate as described previously [3,26], and expressed as picograms per milliliter. IL-1beta concentrations were quantified in the vaginal fluid by commercial ELISA kit (Sanquin, Amsterdam, The Netherlands) and measurements were performed according to the manufacturer's instructions. The intra- and inter-assay coefficient variations were less than 10%. The lower detection limit for human IL-1beta was 1 pg/mL. A zero value was assigned to samples below this limit for statistical calculations. 17 women had undetectable IL-1beta.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of data distribution. IL-1beta concentrations were not normally distributed. Bivariate comparisons, using the Mann-Whitney U test, one-way ANOVA or Kruskal-Wallis non parametric test when appropriate, and chi-squared tests were conducted comparing the IL-1beta tertiles across a wide range of sociodemographic, behavioral and medical characteristics. A univariable multinomial logistic regression model was used to evaluate the odds ratios (ORs) and 95% confidence intervals (CIs) for the IL-1beta tertiles comparing the mutually exclusive adverse outcome categories to term normal births. Univariable logistic regression models were used to evaluate the OR's and 95% CI's for the IL-1beta tertiles comparing the combined adverse categories to the term normal births. A multivariable multinomial regression model was used to evaluate the relative risk ratios (RRRs) and the 95% CIs for the covariates from Table 1 with the middle tertile as the comparison group. Covariates that were significant at the 0.10 level were included in the regression model.

Table 1: Sociodemographic characteristics of women in the first, second and third tertile of IL-1beta concentrations, and comparison between women with lower, middle or upper tertile.

Variable	First tertile n = 133	Second Tertile n = 133	Third Tertile n = 134	P
Age—mean years (SD)	24.8 (5.7)	24.9 (5.7)	23.7 (4.6)	0.116
Race—no. (%)				**0.021**
Black	94 (70.9)	100 (75.2)	78 (58.2)	
White	7 (5.3)	3 (2.3)	5 (3.7)	
Hispanic	32 (24.1)	30 (22.6)	51 (38.1)	
Education—no. (%)				0.08
Did not complete high school	43 (32.3)	42 (31.6)	55 (41.0)	
High School Graduate/GED	59 (44.4)	59 (44.4)	63 (47.0)	
Continued past high school	31 (23.3)	32 (24.1)	16 (11.9)	
Marital status, married—no. (%)	32 (24.1)	24 (18.1)	38 (28.4)	0.136
Non-US born—no. (%)	18 (13.5)	22 (16.5)	38 (28.4)	**0.005**
Parity—no. (%)				0.104
None	51 (38.4)	65 (48.9)	51 (38.1)	
One	33 (24.8)	38 (28.6)	38 (28.4)	
Two or more	49 (36.8)	30 (22.6)	45 (33.6)	
Annual income—mean dollars (SD)	12564 (11434)	11375 (9525)	11433 (10539)	0.570
Body mass index —mean kg/m^2 (SD)	27 (8)	27 (6)	26 (6)	0.599
Gestational age at enrollment—mean weeks (SD)	12.2 (3.7)	11.0 (3.2)	12.7 (3.8)	**<0.001**
Gestational age at delivery—mean weeks (SD)	35.9 (8.1)	35.5 (8.5)	36.9 (6.9)	0.337
Smoked during pregnancy—no. (%)	28 (21.1)	31 (23.3)	23 (17.2)	0.453
Antibiotics use between enrollment and delivery—no. (%)	63 (47.4)	73 (54.9)	59 (44.0)	0.192
Douching in the year before pregnancy—no. (%)	67 (50.3)	68 (51.1)	68 (50.7)	0.993

Previous use of oral contraception in the year before pregnancy—no. (%)	28 (21.1)	21 (15.8)	24 (17.9)	0.535
Ever had sexually transmitted disease—no. (%)	50 (37.6)	61 (45.9)	45 (33.6)	0.111
Sexually transmitted disease in current pregnancy —no. (%)	28 (21.1)	22 (16.5)	42 (31.3)	**0.013**
Trichomonas vaginalis	18 (13.5)	12 (9.0)	26 (19.4)	**0.043**
Chlamydia trachomatis	11 (8.2)	7 (5.2)	18 (13.4)	0.053
Candida spp.	28 (21.1)	33 (24.8)	26 (19.4)	0.563
Nugent score in current pregnancy—mean no. (SD)	8.7 (1.1)	8.9 (1.1)	8.5 (1.0)	**0.034**
Ever had bacterial vaginosis—no. (%)	30 (22.6)	27 (20.3)	21 (15.6)	0.350
Age of sexual debut—mean years (SD)	15.5 (1.9)	15.6 (2.3)	15.9 (2.7)	0.457
Number of partners lifetime—mean number (SD)	5.6 (5.5)	6.7 (6.5)	6.2 (10.8)	0.535

GED: General Equivalency Degree

This research was approved by the institutional review boards at Thomas Jefferson University, Drexel University College of Medicine, and at University of Udine.

Results

Among the 3,915 women attending their first prenatal visit, 1,965 met criteria for eligibility. Of these women, 1,806 (91.9%) consented to participate. A total of 800 (44.3%) study participants were diagnosed with BV (69.3% of black women, and 30.6% of non-black women) and data on birth outcome were available for 707 women (88.4%). Of these BV-positive women, 116 had a preterm adverse pregnancy outcome and 591 had a full term delivery (≥37 weeks). Nine women were excluded for poor specimen quality or missing data, leaving 105 specimens from women with any preterm adverse outcome available for IL-1beta analyses. Specifically, the 105 preterm adverse deliveries included all live PTBs (20 to <37 weeks of gestation, n = 66, of which 52 were spontaneous PTBs, 12 were indicated PTBs, and 2 cases of undefined PTBs because of absence of precise records about induction), stillbirths (20 to <37 weeks of gestation, n = 8), late miscarriages (12 to <20 weeks of gestation, n = 14), and early miscarriages (<12 weeks of gestation, n = 17). Among the 52 spontaneous preterm births, 33 were late SPTB (34 to <37 weeks' gestation), and 19 were early SPTB (20 to <34 weeks' gestation). To ensure a minimum case-control ratio of 1:3, we randomly selected 295 term, normal birth weight deliveries (≥37 weeks and ≥2500 g) from the 591 full term births to serve as controls. The total sample size for these analyses was 400.

The sample consisted mostly of poor, young, unmarried, African American women with relatively low educational attainment enrolled in approximately their 12th week of pregnancy (mean 12 ± SD 3.7 weeks; range, 5-19 weeks of gestation) (Table 1). Ninety-six percent (383/400) of the study participants (all having Nugent 7-10) had detectable IL-1beta concentrations (≥1 pg/mL). Highest value of IL-1beta was 7125 pg/mL. The 33rd percentile (first tertile) corresponded to 106 pg/mL, the 66th percentile (second tertile) corresponded to 396 pg/mL. Table 1 shows comparison of sociodemographic and pregnancy outcomes characteristics according to IL-1beta tertile concentrations. The higher tertile values were more frequently found in Hispanic women (45%, 51/113) than in black women (28.7%, 78/272). On the opposite, the lower tertile values were more frequent in blacks (34.6%, 94/272) than in Hispanics (28.3%, 32/113). Consistently, (median, range) continuous IL-1beta concentrations were lower in blacks (171, 0-4640 pg/mL) than in Hispanics (331, 0-4748 pg/mL), P = 0.005. Hispanics concentrations did not differ from whites (253, 27-2869 pg/mL), P = 0.68. Overall, blacks differed from non-blacks (P = 0.039). Race, foreign born, gestational age at enrollment, Nugent score, and sexually transmitted diseases (particularly *Trichomonas vaginalis*) were associated with the IL-1beta tertiles at the 0.05 level (Table 1).

According to previous observations [35] and data presented in Table 1, vaginal IL-1beta levels can be modulated by the presence of concurrent infections, particularly *T. vaginalis* co-infection, thus a secondary analysis was performed by excluding the 56 women with *T. vaginalis*. Table 2 illustrates the comparison of IL-1beta tertiles among *T. vaginalis* negative women. Differences in race, US born, gestational age at enrollment remain statistically significant, on the contrary STD in current pregnancy was no longer significant. However, ever had an STD and antibiotic use between enrollment and delivery were marginally associated with IL-1beta tertiles (P = 0.06, and P = 0.07, respectively). Specifically, regarding race differences, the higher tertile values were more frequently found in Hispanic women (45.4%, 49/108) than in black women (24.4%, 54/221). On the opposite, the lower tertile values were more frequent in blacks (35.7%, 79/221) than in Hispanics (26.6%, 29/108). Notably, after exclusion of *T. vaginalis* positive women (Table 2), low Nugent score was no longer associated to the highest IL-1beta tertile (Table 1). This finding is in keeping with a previous observation demonstrating a lower Nugent score in BV-positive women co-infected with *T. vaginalis*, who rarely have *Mobiluncus* spp. present in their Gram stain [33].

Table 3 shows results obtained when a multinomial logit regression model was fit to the data with interaction terms of race and nativity in the model. The middle tertile was used as the base group in the model. The foreign born Hispanic group compared to US born black group is associated to a relative risk ratio (RRR)

= 2.51 (1.09-5.76) with the highest tertile after adjusting for age, marital status, education, parity, antibiotic use prior to labor and delivery, gestational age at enrollment and STD's (including *T. vaginalis*) in pregnancy. Age at enrollment was associated with the higher tertile and suggests a lower risk of achieving the highest tertile of IL-1beta compared to the middle tertile with increasing age. Antibiotic use prior to labor and delivery was associated with the higher tertile and suggests a lower risk of achieving the highest tertile for those who used antibiotics during the specified period. Parity was associated with both the lowest and highest tertiles with those having 2 or more children at a higher risk of the extreme tertiles. Gestational age at enrollment was associated with both the lowest and the highest tertiles with increasing gestational age showing an increased risk for both the extreme tertile categories. Having an STD during pregnancy was associated with an elevated risk of the highest tertile and marginally with the lower tertile compared to the middle tertile.

Table 4 shows the odd ratios (OR's) and 95% CI's for the IL-1beta tertiles comparing the adverse birth outcomes to term normal births. The IL-1beta tertiles were not associated with any of the adverse birth outcomes. Also after exclusion of *T. vaginalis* positive women, the results did not show any association between the IL-1beta tertiles and adverse birth outcomes (data not shown).

Table 2: Sociodemographic characteristics of women in the first, second and third tertile of IL-1beta concentrations, and comparison between women with lower, middle or upper tertile after exclusion of 56 *T. vaginalis* positive women.

Variable	First tertile n = 115	Second Tertile n = 121	Third Tertile n = 108	P
Age—mean years (SD)	25.2 (5.8)	25.2 (5.8)	23.6 (4.6)	0.100
Race—no. (%)				**0.002**
Black	79 (68.7)	88 (72.7)	54 (50)	
White	7 (6.1)	3 (2.5)	5 (4.6)	
Hispanic	29 (25.2)	30 (24.8)	49 (45.4)	
Education—no. (%)				0.101
Did not complete high school	35 (30.4)	37 (30.6)	47 (43.5)	
High School Graduate/GED	51 (44.4)	55 (45.5)	46 (42.6)	
Continued past high school	29 (25.2)	29 (23.9)	15 (13.9)	
Married	31 (26.9)	24 (19.8)	34 (31.5)	0.126
Non US born—no. (%)	16 (13.9)	22 (18.2)	36 (33.3)	**0.001**
Parity—no. (%)				0.104
None	42 (36.5)	58 (47.9)	41 (37.9)	
One	27 (23.5)	34 (28.1)	31 (28.7)	
Two or more	46 (40.0)	29 (23.9)	36 (33.3)	
Annual income—mean dollars (SD)	13301 (12372)	11264 (9667)	11159 (11159)	0.359
Body mass index —mean kg/m^2 (SD)	27.2 (8.2)	27 (5.8)	26.1 (5.6)	0.437
Gestational age at enrollment—mean weeks (SD)	12.0 (3.80)	11.0 (3.3)	12.7 (3.9)	**0.002**
Gestational age at delivery—mean weeks (SD)	35.9 (8.1)	35.3 (8.8)	36.9 (7.2)	0.329
Smoked during pregnancy—no. (%)	23 (20)	31 (25.6)	18 (16.7)	0.240
Antibiotics use between enrollment and delivery—no. (%)	48 (45.3)	62 (54.4)	39 (38.6)	0.070
Douching in the year before pregnancy—no. (%)	59 (51.3)	59 (48.8)	55 (50.9)	0.915
Previous use of oral contraception in the year before pregnancy—no. (%)	22 (19.1)	21 (17.4)	22 (20.4)	0.842
Ever had sexually transmitted disease—no. (%)	41 (35.7)	53 (43.8)	31 (28.7)	0.060
Sexually transmitted disease in current pregnancy —no. (%)	10 (8.7)	10 (8.7)	16 (14.8)	0.203

Trichomonas vaginalis	-	-	-	-
Chlamydia trachomatis	9 (7.0)	6 (5.1)	12 (11.4)	0.219
Candida spp.	24 (21.1)	27 (22.9)	18 (17.1)	0.560
Nugent score in current pregnancy—mean no. (SD)	8.7 (1.1)	8.8 (1.1)	8.6 (1.0)	0.341
Ever had bacterial vaginosis—no. (%)	24 (20.9)	24 (19.8)	13 (12.0)	0.170
Age of sexual debut—mean years (SD)	15.5 (1.9)	15.7 (2.3)	15.9 (2.8)	0.385
Number of partners lifetime—mean number (SD)	5.8 (5.8)	6.7 (6.7)	6.3 (11.9)	0.735

GED: General Equivalency Degree

Table 3: Relative risk ratios (RRR's) and 95% confidence intervals (CI's) for the association between IL-1beta concentration levels and significant covariates.

Variable	IL-1beta <33rd percentile RRR (95% CI)	IL-1beta >66th percentile RRR (95% CI)
Age, y	0.97 (0.92-1.03)	**0.93 (0.87-0.99)**
Married	1.58 (0.77-3.24)	1.42 (0.67-2.98)
Antibiotics prior to labor and delivery	0.61 (0.34-1.07)	**0.50 (0.27-0.92)**
US born black	1	1
US born Hispanic	1.52 (0.65-3.57)	1.52 (0.60-3.82)
US born White	1.66 (0.36-7.61)	1.54 (0.29-7.91)
Foreign born black	0.48 (0.10-2.24)	0.44 (0.07-2.65)
Foreign born Hispanic	0.67 (0.27-1.67)	**2.51 (1.09-5.76)**
Education-post high school	1	1
Education-high school	0.71 (0.36-1.41)	1.45 (0.65-3.26)
Education-less than high school	0.70 (0.32-1.49)	1.48(0.62-3.50)
Parity-none	1	1
Parity-1	1.35 (0.69-2.65)	1.95 (0.97-3.91)
Parity-2 or more	**2.78 (1.32-5.85)**	**3.45 (1.56-7.62)**
Gestational age at enrollment, wk	**1.10 (1.01-1.18)**	**1.14 (1.06-1.23)**
STD during pregnancy	1.99 (0.97, 4.07)	**3.70 (1.79-7.65)**

Table 4: Crude odds ratios (OR's) and 95% CI's for the association between IL-1beta concentration levels and adverse preterm birth outcome (n = 105).

Pregnancy Outcome	Total n = 400	IL-1beta <33rd percentile, n = 133		IL-1beta 33rd-<66th percentile, n = 133		IL-1beta >66th percentile, n = 134	
	n	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Term normal birth weight[a]	295						
All adverse preterm outcomes	105	34	0.80 (0.47-1.37)	40	1	31	0.70 (0.41-1.21)
Early miscarriage (<12 weeks)	17	6	0.81 (0.26-2.48)	7	1	4	0.52 (0.15-1.81)
Late miscarriages (12-<20 weeks)	14	6	1.12 (0.33-3.81)	5	1	3	0.54 (0.13-2.33)
Early spontaneous preterm births (20-<34 weeks)[b]	19	4	0.42 (0.12-1.40)	9	1	6	0.60 (0.21-1.76)
Late spontaneous preterm births (34-<37 weeks)[c]	33	10	0.85 (0.35-2.10)	11	1	12	0.98 (0.41-2.34)

All spontaneous preterm births[d]	52	14	0.66 (0.31-1.38)	20	1	18	0.81 (0.41-1.63)
Indicated preterm births[d]	12	6	1.88 (0.46-7.73)	3	1	3	0.90 (0.18-4.58)
Stillbirths	8	2	0.47 (0.08-2.62)	4	1	2	0.45 (0.08-2.52)

[a]Term normal birth weight deliveries group: livebirths ≥37 weeks of gestation and birth weight ≥2500 g (control group).

[b]Spontaneous live preterm deliveries between 20 to <34 weeks of gestation.

[c]Spontaneous live preterm deliveries between 34 to <37 weeks of gestation.

[d]Two PTB cases did not have enough information to be classified as spontaneous or indicated PTBs and hence were dropped from the analysis.

Continuous values of IL-1beta concentrations did not vary (by Mann-Whitney test) between: a) all adverse preterm outcomes vs. controls in all participants (P = 0.32); b) in black only women (P = 0.94); c) in Hispanic only women (P = 0.46); d) in white only women (P = 0.47).

Frequency of all adverse birth outcomes were different between the races with 30.5% (83/272) of blacks, 16.8% (19/113) of Hispanic, and 20% (3/15) of whites having an adverse outcome, P = 0.016. The race comparisons were not significant for the term normal weight controls and spontaneous PTB alone (P = 0.057) and for all adverse outcomes categorized into the mutually exclusive categories (P = 0.30).

Discussion

This study in the largest investigation regarding vaginal IL-1beta performed in pregnant women who were BV-positive enrolled in early gestation. More than 1 million infants die every year because they are born preterm [8,48]. PTB is an increasingly prevalent, complex condition associated with a high risk of infant mortality and morbidity, including cerebral palsy, blindness, hearing loss, and also hidden disabilities such as school difficulties and behavioural problems that become apparent and persist into adolescence [49]. PTB has a recognized complex multifactorial etiology. Numerous clinical studies have shown a direct relationship between reproductive tract infection/inflammation and PTB [7,9,10]. Among microbial alterations, BV has received particular attention, because it is a highly prevalent condition among childbearing and pregnant women, with prevalence ranging from approximately 10 to 50% according mainly to ethnic origin, with black women showing the highest prevalence.[50,51] However, conflicting findings in large-scale clinical trials on the PTB prevention effects of intensive antibiotic treatments has been a topic of much debate [23,24,52,53]. Recently, many authors call for the development of biomarkers to assess risk of adverse pregnancy outcomes early in gestation in BV-positive women at high risk of adverse pregnancy outcome [2-4,47,54,55]. Among candidate biomarkers, inflammatory factors seem promising owing to the evidence implicating of inflammatory pathways in PTB and labor (such as the infiltration by macrophages and neutrophils into the myometrium and cervix) [44,56].

IL-1beta is a particularly attractive pathophysiologic marker due to the availability of a recombinant form of the IL-1 receptor antagonist, called anakinra, which has been shown to block IL-1beta pro-inflammatory effects in different diseases [41,57]. Levels of IL-1beta in vaginal fluid are 10 to 20-fold elevated in BV positive women compared to controls. Interestingly, recent evidence suggests that genetic variants in IL-1 genes are associated with BV [35], as well as to spontaneous preterm labor [58]. Because results support a central role of IL-1beta, which appeared to be over stimulated in BV, if PTB would be associated with elevated local IL-1beta, its specific blockade using anakinra thereby could potentially open new therapeutic avenues in PTB. Thus, vaginal IL-1beta appears to be a suitable predictor of risk for PTB among BV-positive women. In spite of this rationale, we did not observe any association between IL-beta levels and PTB, nor adverse pregnancy outcomes, in general. We explored both high levels (upper tertile) and low levels (lower tertile) of IL-1beta, because both extreme conditions could be detrimental. However, none of the extreme levels were associated with increased risk of adverse outcome.

Reasons for failure of vaginal IL-1beta to predict PTB could derive mainly from:

A. Other immune factors down-stream from IL-1beta stimulus are more crucial than IL-1beta itself;

B. Vaginal IL-1beta levels are unrelated to upper genital tract inflammation and do not reflect for example amniotic fluid IL-1beta levels;

C. Timing of optimal vaginal IL-1beta use to predict PTB is later in gestation [59,60], and/or a more narrow weeks of gestation interval should be considered for inclusion;

D. IL-1beta is one too general immune factor, modulated by almost every kind of stimuli including mechanical ones, thus it is not truly indicative of infection related damages.

An interesting finding of our research is race modulation of vaginal IL-1beta levels, this adds to the evidence for a role of ethnic background when considering cytokine profile [61-64], which likely derives from differences in genetic polymophisms of IL-1 family genes [63,65]. Overall, this variation may lead to different pathophysiologic pathways of PTB in different races [66,67].

An intriguing observation of our study is that women in the middle tertile of IL-1beta were enrolled on average 1 week earlier that women in the extreme tertiles, this seems to suggest that with progression of gestation hyper- and hypo-responders become more evident. In the multivariable multinomial regression model parity (2 or more) was also a risk factor for membership in an extreme tertiles of IL-1beta. Potentially this finding results from a memory effect of past hyper- and hypo-responder in prior gestations. Further investigations are needed to assess these issues.

We also observed that being non-US born especially if of Hispanic race increases the likelihood of being an IL-1beta hyper-responders. Possibly this result derives from different exposures over the life course up-regulating the inflammatory response. No previous study examined this kind of effects, thus, more detailed studies will be necessary to address this issue.

An obvious limitation of our study is that, due to the project design aimed to identify BV subgroups at high risk of adverse pregnancy outcomes, only BV-positive women were examined. Further cohort studies enrolling women regardless of BV-status could assess in the general population of pregnant women the risk associated to vaginal IL-1beta levels.

Among previous studies that examined cervicovaginal cytokine association with adverse pregnancy outcomes, Genc and colleagues showed that among women colonized with anaerobic Gram-negative rods and/or *Gardnerella vaginalis*, an elevated IL-1beta concentration was associated with preterm delivery [68]. On the other hand, a study including 121 women with twin pregnancies sampled at 24, 26, 28, 30, 32 and 34 weeks of gestation determined that the levels of IL-1alpha and IL-6 in cervicovaginal secretion were not significantly associated with preterm birth [37].

The availability of non-invasive early markers that could predict adverse pregnancy outcomes would be very helpful in guiding management of BV positive women remote from term. Ideally, to be useful clinically, predictive markers of pregnancy complications should discriminate between women who will and will not have a specific adverse outcome, far before the outcome occurs to possibly guide pharmacological treatments. In this study, we have found that, although IL-1beta is a prominent cytokine in secretions of BV positive women, it does not constitute a predictive marker of adverse outcome. Our study is in line with recent findings by other authors measuring plasma cytokine profile in pregnant women [69]. None of the measured cytokines demonstrated high sensitivity, specificity, or discriminative predictive values for any outcome. Overall, it is likely that inability of cytokines to constitute a valid biomarker of risk reflects the significant overlap in levels associated to each risky condition. Future studies should be devoted to examine cytokines levels in combinations with other kind of markers such as microbial factors.

Clinical Implications

Concentration of IL-1beta in vaginal fluid at 12 weeks' gestation is not a predictive marker for adverse pregnancy outcomes including miscarriage and spontaneous preterm birth. Several evidence suggests immune response, particularly innate immunity as a crucial component of complex events leading to adverse pregnancy outcomes and particularly spontaneous PTB, thus more research exploring immune factors and single or combined biomarkers is advisable. In general, further research should include investigations of low-cost, non-invasive and effective tests and treatments to reduce (or at least delay) spontaneous preterm birth and reduce the risk of perinatal mortality/morbidity arising from preterm birth, thus attenuating major familial distress and health costs.

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