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Effect of Antibiotic Exposure on Nugent Score Among Pregnant Women With and Without Bacterial Vaginosis

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Abstract

Objective—To evaluate whether vaginal flora is altered by antibiotic exposure and associated with a risk of preterm birth, particularly among women with initially normal vaginal flora.

Methods—This was a secondary analysis of a randomized trial of metronidazole and erythromycin for the prevention of preterm birth among women with a positive fetal fibronectin test. Vaginal swabs for Nugent Gram stain score were collected for classification of bacterial vaginosis before and after antibiotic exposure and read at a central laboratory. Change in Nugent score was assessed for women with (score 7 or higher) or without (score lower than 7) bacterial vaginosis. Linear regression analysis evaluated whether change in Nugent score was associated with preterm birth.

Results—Two-hundred women without and 69 women with bacterial vaginosis had Gram stain performed before and after antibiotic therapy. Median Nugent score for all women declined from 4.0 to 2.0 after antibiotic therapy, $p < 0.001$. Nugent score declined both for those without (from 2.0 to 1.5, $p = 0.11$) and more dramatically, those with bacterial vaginosis (from 8.0 to 3.0, $p < 0.01$). The components of the Nugent score that were affected by antibiotic exposure were similar among women with and without bacterial vaginosis. Antibiotic exposure and the change in Nugent score were unrelated to preterm birth among bacterial vaginosis-negative women.

Conclusion—Antibiotic exposure is not associated with preterm birth and does not worsen Nugent score among women with normal vaginal flora and positive fetal fibronectin.

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*For a list of other members of the NICHD MFMU, see the Appendix online at <http://links.lww.com/xxx>.

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Introduction

Multiple studies have examined the frequency of preterm birth with the use of antibiotic therapy. These studies have varied in design and approach. Some studies have evaluated antibiotics targeted at specific pathogens, (6, 9, 11, 17) whereas others have investigated agents not specifically targeted at candidate pathogenic flora.(2, 3, 5, 14) The results of studies of antibiotic use to prevent preterm birth have been largely disappointing.(3, 11, 16) The majority shows no benefit of therapy and some even suggest that antibiotic use is associated with an increased frequency of preterm birth.(1, 8, 9, 14, 15, 18) In fact, two separate randomized trials examining the use of metronidazole in pregnancy(9, 14) and one using it prior to conception(2) showed an increase in preterm birth with the use of therapy.

If antibiotic use increases the frequency of preterm birth, the mechanism by which this occurs is unknown. One hypothesis holds that antibiotic therapy may alter vaginal flora and predispose to preterm birth. Carey and Klebanoff conducted a retrospective analysis of vaginal cultures collected as part of the Vaginal Infections and Prematurity (VIP) study. They found that alterations in vaginal flora increased the risk of preterm birth with an adjusted odds ratio of 2.99, 95% CI (1.37-6.53).(4) One mechanism by which this might occur is abolition of the most protective vaginal bacteria, hydrogen peroxide-producing lactobacilli. With loss of lactobacilli, there is an opportunity for growth and ascension of more pathogenic bacteria. Hauth et al, however, did not find significant disruption of flora in women treated with antibiotics.(6) Bacterial vaginosis, diagnosed by Amsel's criteria, developed *de novo* in 5% of women who received antibiotics versus 13% of those who received placebo.

The objective of this study was to evaluate whether systemic antibiotic exposure alters normal vaginal flora during pregnancy, as measured by Nugent score, leading to increased risk of preterm birth versus placebo among women with a positive fetal fibronectin test.

Materials and Methods

We performed a secondary analysis of data collected during a randomized trial of metronidazole and erythromycin for the prevention of preterm birth in women with a positive cervicovaginal fetal fibronectin test.(3) At each of 13 participating centers, asymptomatic women were enrolled between 21 weeks 0 days and 25 weeks 6 days gestation. All women enrolled in the study had a positive fetal fibronectin test (> 50 ng/mL). At the screening visit, vaginal swabs were collected for Nugent Gram stain score classification of bacterial vaginosis (BV), and evaluated at a central laboratory.

Women were excluded from the parent trial if they had fetal death, major fetal anomalies, multiple gestation, allergy to study medication, antibiotic use at randomization, use of topical antifungals within 24 hours of screening, vaginal symptoms (unelicited, spontaneously reported vaginal symptoms, including itching, burning, or malodor indicating need for specific treatment), major medical or obstetrical complications, and anticipated prenatal care or delivery at a nonparticipating center.(3) Women with prior preterm birth or other risk factors for preterm birth were not excluded.

The parent trial was approved by each of the institutional reviews boards at the participating sites and all women provided written, informed consent. Women were randomized to either metronidazole 250 mg three times daily plus erythromycin 250 mg four times daily or to matching placebo. The parent trial utilized the simple urn method of randomization with stratification by clinical center. A follow-up visit was scheduled 14 days after randomization during which another swab was collected for Gram stain to assess Nugent score. For the

purposes of this secondary analysis, women were included if they had available Nugent scores for both visits. The main focus of this analysis was those women who had normal vaginal flora and were antibiotic exposed. The placebo group and the groups with bacterial vaginosis were included for comparison.

The primary outcome measure for this analysis was change in Nugent score among women with normal flora exposed to antibiotics. We also evaluated the relationship between this change and the subsequent preterm birth risk. The change in Nugent score was assessed for women with (score ≥ 7) or without (score < 7) BV in a stratified manner. Linear regression analysis was used to evaluate whether change in Nugent score was associated with preterm birth.

The univariable analyses were performed using chi-square and Wilcoxon signed-rank test where appropriate. Logistic regression and calculation of odds ratios were conducted to assess the relationship of the risk of preterm birth and change of Nugent score. Multiple logistic regression was performed to control for potential confounders and did not change the findings (data not shown). Statistical significance was set at $p < 0.05$.

Results

The parent trial was a randomized, double-masked placebo-controlled trial and included 715 women in the intention-to-treat analysis. The flow of patients within the trial has been previously published.⁽³⁾ A total of 547 of 715 women had Nugent scores available from both visits and were included in this analysis. The age, body mass index, racial/ethnic, and demographic characteristics were similar between groups (Table 1). As in previous studies, those with BV were slightly more likely to report black race. There were 388 women who did not and 159 women who did have BV. Of the 388 women who did not have BV, 200 were randomized to antibiotics. Of the 159 women with BV, 69 were in the antibiotic arm. The median Nugent score for all women in the study declined from 4.0 to 2.0 after antibiotic therapy, $p < 0.001$. The primary outcome measure of the study was change in Nugent score among BV negative women exposed to antibiotics. The median score in this group was not worsened by antibiotic exposure, 2.0 to 1.5, $p = 0.11$. The median Nugent score declined more dramatically within the BV positive group (from 8.0 to 3.0, $p < 0.01$), (Table 2).

In order to examine whether antibiotic exposure might influence one particular component of the Nugent score, we determined the change in score component in each of the sub-groups. The components of the Nugent score that were affected by antibiotic exposure were similar among women with and without BV and were primarily reductions in the scores for *G. vaginalis*/anaerobic Gram negative rods and for *Lactobacillus* score. Of the different Gram stain components, *Mobiluncus* was the least impacted by antibiotics. As anticipated, placebo had no apparent effect upon the components of the score among women without BV (Table 3).

Among women with normal flora, antibiotic exposure did not increase the risk of preterm birth (13% vs. 14%, $p = 0.82$) and change in Nugent score was not related to it, with an Odds Ratio, (95% CI): 1.07, (0.9-1.2) for each one-point change in Nugent score. Logistic regression models were fit after stratification by BV status at entry. Neither change in Nugent score nor antibiotic exposure was associated with preterm birth among women with or without BV. As has been consistently demonstrated in other studies, prior spontaneous preterm birth and low pre-pregnancy BMI were associated with preterm birth in this study (data not shown). The mean gestational age at delivery and frequency of preterm birth were not significantly different in any group (Table 4).

Discussion

We did not find significant alteration of vaginal flora due to antibiotic exposure among women with normal flora. While disruption of normal flora has been proposed as a possible mechanism for the recent studies demonstrating an increased risk of preterm birth among women exposed to certain antibiotics, our data do not support this theory. The theory would suggest that a lack of normal flora in the vagina would allow for ascent of pathogenic bacteria into the uterine cavity thus leading to a cascade of inflammatory events culminating in preterm labor and delivery. We found a slight improvement in Nugent score among women with BV who were exposed to antibiotics. This improvement was also demonstrated among women with normal flora although less distinctly compared to those with BV.

We did not find preterm birth to be more common among the women with normal flora exposed to antibiotics. In fact, the rate of preterm birth, ranging from 10-17% between the strata, was not as high as one might expect in a cohort of women with a positive fetal fibronectin test. The reasons for this are unclear and may be related to a “Hawthorne effect”, in which patients engaged in clinical trials have improved outcomes regardless of their study group. The mean gestational age at delivery was at term and was similar among the strata of BV and therapy groups. We were unable to detect an association between change in Nugent score and the occurrence of preterm birth.

The findings of the parent trial for this analysis showed that the rate of preterm birth among women receiving antibiotics was 14.4% compared to 12.4% among those who received placebo. Subsequent secondary analysis of the trial showed that among the subset of women in whom BV actually resolved, the preterm birth rate was decreased(7). Nugent scores were examined as a dichotomous variable for the purposes of that analysis, with BV being defined as present or absent. Nugent et al commented in their original paper that the score could be used as a continuum rather than the forced dichotomy of BV positive or negative.(13) Our analysis treated the score as a continuous variable with the intent of being able to detect more subtle changes among women with normal flora. While we were able to detect more subtle differences in score than the typical dichotomous use of the Nugent score offers, our findings did not translate to clinically significant outcomes.

Strengths of our study include the high quality of data collection with regular edits and audits of data mandated by the study protocol used at all MFMU Network centers. Gram stains and Nugent scores were read at a central laboratory with documented high reproducibility of results. A secondary analysis of the Network “BV” study showed that 78% of women with BV experience resolution with therapy and that there is also spontaneous regression of BV in up to a third of placebo-treated women.(10) Our findings support those results. We observed spontaneous improvement of Nugent score in the placebo-treated arm, from a mean of 8.38 to 7.20. We did not, however, observe improvement in the Nugent score among women with normal flora in the placebo arm. The very slight improvement in Nugent score among those with normal flora exposed to antibiotics was significant, mean 2.37 to 2.05, and likely a reflection of a true improvement due to antibiotic exposure.

This study does not explain the mechanism of preterm birth associated with antibiotic exposure. A number of potential mechanisms are plausible. A commonly cited potential mechanism is the notion that bacteria, when lysed, actually cause an increase in the pro-inflammatory state which might lead to uterine contractions. Another theory is that there could be disruption in normal flora that is not measurable via Nugent score. Our study is limited by its retrospective design and use of a surrogate marker for disruption of flora leading to preterm birth from exposure to antibiotics. More detailed vaginal flora

information was not collected in the original study, so this was not possible given the nature of the secondary analysis. The analysis by Carey and Klebanoff found that in particular, acquisition of *E. coli* or *K. pneumoniae* was an independent risk factor for preterm birth adjusted OR 2.99, 95% CI 1.37-6.53).(4) It has also been suggested that antibiotics may not be adequate therapy for upper tract disease. However, in a secondary analysis of a randomized trial of interconception antibiotics, neither endometrial microbial invasion nor plasma cell endometritis were risk factors for adverse pregnancy outcomes.(19) Alternatively, preterm birth and infections may be markers of an underlying dysfunction in maternal immunity.(4) Such disorders likely have a genetic or epigenetic predisposition. Macones et al found that there was an interaction among carriers of a tumor necrosis factor polymorphism exposed to BV and the risk of preterm birth.(12) Future study of the association between exposure to antibiotics, pathogens, and preterm birth outcomes is necessary to examine these relationships.

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Appendix

In addition to the authors, other members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network are as follows:

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References

1. Anderson BL, Simhan HN, Simons K, Wiesenfeld HC. Additional antibiotic use and preterm birth among bacteriuric and nonbacteriuric pregnant women. *International Journal of Gynaecology and Obstetrics*. 2008; 102(2):141–145. [PubMed: 18555999]
2. Andrews WW, Goldenberg RL, Hauth JC, Cliver SP, Copper R, Conner M. Interconceptional antibiotics to prevent spontaneous preterm birth: a randomized clinical trial. *American Journal of Obstetrics & Gynecology*. 2006; 194:617–23. [PubMed: 16522388]
3. Andrews WW, Sibai BM, Thom EA, Dudley D, Ernest JM, McNellis D, Leveno KJ, Wapner R, Moawad A, O'Sullivan MJ, Caritis SN, Iams JD, Langer O, Miodovnik M, Dombrowski M, National Institute of Child H, Human Development Maternal-Fetal Medicine Units N. Randomized clinical trial of metronidazole plus erythromycin to prevent spontaneous preterm delivery in fetal fibronectin-positive women. *Obstetrics & Gynecology*. 2003; 101:847–55. [PubMed: 12738139]
4. Carey JC, Klebanoff MA. Is a change in the vaginal flora associated with an increased risk of preterm birth? *American Journal of Obstetrics & Gynecology*. 2005; 192:1341–6. [PubMed: 15846235]
5. Goldenberg RL, Mwatha A, Read JS, Adeniyi-Jones S, Sinkala M, Msmanga G, Martinson F, Hoffman I, Fawzi W, Valentine M, Emel L, Brown E, Mudenda V, Taha TE, Hptn T. The HPTN 024 Study: the efficacy of antibiotics to prevent chorioamnionitis and preterm birth. *American Journal of Obstetrics & Gynecology*. 2006; 194(3):650–61. [PubMed: 16522393]
6. Hauth JC, Goldenberg RL, Andrews WW, DuBard MB, Copper RL. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *New England Journal of Medicine*. 1995; 333:1732–6. [PubMed: 7491136]
7. Hendler I, Andrews WW, Carey CJ, Klebanoff MA, Noble WD, Sibai BM, Hillier SL, Dudley D, Ernest JM, Leveno KJ, Wapner R, Iams JD, Varner M, Moawad A, Miodovnik M, O'Sullivan MJ, Van Dorsten PJ, National Institute of Child Health and Human Development M-FMUN. The relationship between resolution of asymptomatic bacterial vaginosis and spontaneous preterm birth in fetal fibronectin-positive women. *Am J Obstet Gynecol*. 2007; 197(5):488.e1–5. [PubMed: 17980184]
8. Kigozi GG, Brahmbhatt H, Wabwire-Mangen F, Wawer MJ, Serwadda D, Sewankambo N, Gray RH. Treatment of *Trichomonas* in pregnancy and adverse outcomes of pregnancy: A subanalysis of a randomized trial in Rakai, Uganda. *Am J Obstet Gynecol*. 2003; 189:1398–1400. [PubMed: 14634576]
9. Klebanoff MA, Carey JC, Hauth JC, Hillier SL, Nugent RP, Thom EA, Ernest JM, Heine RP, Wapner RJ, Trout W, Moawad A, Leveno KJ, Miodovnik M, Sibai BM, Van Dorsten JP, Dombrowski MP, O'Sullivan MJ, Varner M, Langer O, McNellis D, Roberts JM, National Institute of Child H, Human Development Network of Maternal-Fetal Medicine U. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic *Trichomonas vaginalis* infection. *New England Journal of Medicine*. 2001; 345:487–93. [PubMed: 11519502]
10. Klebanoff MA, Hauth JC, MacPherson CA, Carey JC, Heine RP, Wapner RJ, Iams JD, Moawad A, Miodovnik M, Sibai BM, vanDorsten JP, Dombrowski MP, National Institute for Child Health and Development Maternal Fetal Medicine Units N. Time course of the regression of

- asymptomatic bacterial vaginosis in pregnancy with and without treatment. *Am J Obstet Gynecol.* 2004; 190(2):363–70. [PubMed: 14981375]
11. Klebanoff MA, Regan JA, Rao AV, Nugent RP, Blackwelder WC, Eschenbach DA, Pastorek JG 2nd, Williams S, Gibbs RS, Carey JC. Outcome of the Vaginal Infections and Prematurity Study: results of a clinical trial of erythromycin among pregnant women colonized with group B streptococci. *American Journal of Obstetrics & Gynecology.* 1995; 172:1540–5. [PubMed: 7755068]
 12. Macones GA, Parry S, Elkousy M, Clothier B, Ural SH, Strauss JF. A polymorphism in the promoter region of TNF and bacterial vaginosis: preliminary evidence of gene-environment interaction in the etiology of spontaneous preterm birth. *American Journal of Obstetrics and Gynecology.* 2004; 190(6):1504–1508. [PubMed: 15284722]
 13. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *Journal of Clinical Microbiology.* 1991; 29:297–301. [PubMed: 1706728]
 14. Shennan A, Crawshaw S, Briley A, Hawken J, Seed P, Jones G, Poston L. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMETS Study. *British Journal of Obstetrics and Gynaecology.* 2006; 113:65–74. [PubMed: 16398774]
 15. Shennan A, Crawshaw S, Briley A, Hawken J, Seed P, Jones G, Poston L. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMETS Study. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2006; 113(1):65–74. [PubMed: 16398774]
 16. Thinkhamrop J, Hofmeyr GJ, Adetoro O, Lumbiganon P. Prophylactic antibiotic administration in pregnancy to prevent infectious morbidity and mortality. *Cochrane Database of Systematic Reviews.* 2002; (4) CD002250.
 17. Thomsen AC, Morup L, Hansen KB. Antibiotic elimination of group-B streptococci in urine in prevention of preterm labour. *Lancet.* 1987; 1(8533):591–3. [PubMed: 2881132]
 18. Tita ATN, Cliver SP, Goepfert AR, Conner M, Goldenberg RL, Hauth JC, Andrews WW. Clinical trial of interconceptional antibiotics to prevent preterm birth: subgroup analyses and possible adverse antibiotic-microbial interaction. *Am J Obstet Gynecol.* 2007; 197(4):367.e1–6. [PubMed: 17904962]
 19. Tita ATN, Cliver SP, Goepfert AR, Conner M, Goldenberg RL, Hauth JC, Andrews WW. Clinical trial of interconceptional antibiotics to prevent preterm birth: subgroup analyses and possible adverse antibiotic-microbial interaction. *American Journal of Obstetrics and Gynecology.* 2007; 197(4):367.e1–367.e6. [PubMed: 17904962]

Table 1

Demographic characteristics of subjects by BV status and antibiotic exposure

Demographic characteristic	BV negative		BV positive	
	Placebo	Antibiotic exposed	Placebo	Antibiotic exposed
n	188	200	90	69
Age, Mean (+/- sd)	23.8 ± 5.5	24.9 ± 5.7	22.7 ± 4.6	23.0 ± 5.0
Pre-pregnancy BMI, Mean (+/- sd)	24.9 ± 5.9	24.8 ± 5.7	23.8 ± 4.8	24.9 ± 5.6
Race/Ethnicity, n (%)				
Black	82 (43.6%)	80 (40.0%)	49 (54.4%)	41 (59.4%)
White	41 (21.8%)	38 (19.0%)	8 (8.9%)	6 (8.7%)
Hispanic	64 (34.0%)	77 (38.5%)	30 (33.3%)	19 (27.5%)
Government-assisted insurance, n (%)	137 (72.9%)	141 (70.5%)	71 (78.9%)	55 (79.7%)
Tobacco in pregnancy, n (%)	34 (18.1%)	25 (12.5%)	12 (13.3%)	15 (21.7%)
Nulliparity, n (%)	89 (47.3%)	78 (39%)	39 (43.3%)	28 (40.6%)
Prior spontaneous PTB, n (%)	26 (13.8%)	20 (10%)	13 (14.4%)	4 (5.8%)
Married, n (%)	87 (46.3%)	110 (55.0%)	33 (36.7%)	24 (34.8%)
Education level, Mean (+/- sd)	11.1 ± 2.5	11.2 ± 2.8	10.4 ± 2.6	10.8 ± 2.2

BV: bacterial vaginosis, sd: standard deviation, BMI: body mass index, PTB: preterm birth

Table 2

Median Nugent scores at enrollment and follow-up

	BV–		BV+	
	Placebo	Antibiotics	Placebo	Antibiotics
Nugent at enrollment, Median (range)	2.0 (0-4.0)	2.0 (0-4.0)	8.0 (8.0-9.0)	8.0 (8.0-9.0)
Nugent at follow-up, Median (Range)	2.0 (0-4.0)	1.5 (0-3.0)	8.0 (6.0-9.0)	3.0 (1.0-7.0)
p value *	0.94	0.11	<0.01	<0.01

BV: bacterial vaginosis

* Wilcoxon signed-rank test

Table 3

Changes in components of Nugent score following administration of study drug

Components	BV–		BV+	
	Placebo Median (range) p value	Antibiotics Median (range) p value	Placebo Median (range) p value	Antibiotics Median (range) p value
<i>Lactobacillus</i>	0 (0, 0) 0.87	0 (–1, 0) 0.06	0 (–2, 0) <0.01	–3 (–4, –1) <0.01
<i>G. Vaginalis/ Anaerobic</i>	0 (–0.5, 1.0)	0 (–1, 0)	0 (0, 0)	–2 (–3, 0)
<i>Gram negative rods</i>	0.35	0.10	<0.01	<0.01
<i>Mobiluncus</i>	0 (0, 0) 0.06	0 (0, 0) 0.50	0 (0, 0) 0.09	0 (0, 2) <0.01
Total	0 (–1, 1) 0.71	0 (–2, 1) 0.03	0 (–2, 0) <0.01	–6 (–7, –2) <0.01

BV: bacterial vaginosis, *G. vaginalis*: *Gardnerella vaginalis*

Test of significance for change in each component by the Wilcoxon signed-rank test

Table 4

Gestational age at delivery and rate of preterm birth by group

	BV–			BV+		
	Placebo	Antibiotics	p value	Placebo	Antibiotics	p value
Gestational age at delivery[*], mean (+/- sd)	38.3 (+/-2.5)	38.4 (+/-2.6)	0.59	38.3 (+/-2.3)	38.7 +/- (1.8)	0.55
Preterm birth <37 weeks[†], n(%)	26 (14)	26 (13)	0.82	15 (17)	7 (10)	0.21

BV: bacterial vaginosis

^{*} Wilcoxon rank sum test[†] Chi-square test