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Additional antibiotic use and preterm birth among bacteriuric and nonbacteriuric pregnant women *

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Abstract

Objective—To determine the risk of preterm birth related to use of additional antibiotics.

Methods—Women with Group B streptococcal (GBS) bacteriuria and women with negative urine cultures in a hospital-wide research registry were included. The impact of prenatal antibiotics in addition to those used to treat GBS bacteriuria was assessed. Logistic regression was used to determine the risk of preterm birth among bacteriuric women who received “other antibiotics”.

Results—A total of 203 women with GBS bacteriuria and 220 women with negative cultures were included. The frequency of preterm birth was 16% (35/220) for women in the control group, 16% (19/120) for women with bacteriuria not receiving additional antibiotics, and 28% (23/83) for women with bacteriuria who received antibiotics for “other indications”. Among women with GBS bacteriuria, the risk of preterm birth was increased with the use of “other antibiotics” (adjusted odds ratio, 2.7; 95% confidence interval, 1.2–6.1).

Conclusion—Among women with GBS bacteriuria, exposure to additional antibiotics is associated with an increased risk of preterm birth.

Keywords

Antibiotics; Bacteriuria; Group B streptococcus; Pregnancy; Preterm birth

1. Introduction

According to data reported by the March of Dimes, over a 10-year period from 1994 to 2004 preterm birth did not decrease in the United States and actually appeared to be increasing slightly [1]. Likewise, infant mortality resulting from preterm birth, an important indicator of consequence, did not decrease over the period from 1996 to 2002. In fact, preterm birth is the second leading cause of neonatal mortality after congenital anomalies [1]. While significant

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Synopsis: Additional antibiotic use is associated with an increased risk of preterm birth among women with Group B streptococcal bacteriuria independent of treatment for bacteriuria.

attention has been given to the problem of preterm birth, there has been little progress in decreasing its occurrence.

Because of the association of infections with preterm birth, considerable attention has been paid to amniotic fluid infection and sexually transmitted infections [2–7]. 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 [8–11], whereas others have trialed agents not specifically targeted at candidate pathogenic flora [12–15]. One area showing evidence of improvement with the use of antibiotics is the treatment of asymptomatic bacteriuria [10,16]. The results of other studies of antibiotic use to prevent preterm birth have been largely disappointing [11,13,17]. The majority show no benefit of therapy and some even suggest that antibiotic use is associated with increased frequency of preterm birth [9,15,18].

The mechanism by which antibiotic use might increase the frequency of preterm birth is unknown. Antibiotic therapy may alter vaginal flora and predispose preterm birth. Carey and Klebanoff [19] 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). They also found that metronidazole use prior to 32 weeks of gestation was associated with preterm birth. The aim of the present study was to determine if receipt of antibiotics in addition to those provided for bacteriuria was associated with preterm birth among a retrospective cohort of women.

2. Materials and methods

Secondary analysis of a retrospective cohort was performed. The original study found that lack of treatment of GBS bacteriuria early in pregnancy is associated with chorioamnionitis at delivery [20]. The Magee-Womens Hospital Women and Infants Research Registry was used for the study. This is a voluntary registry that was created to allow screening of charts for research purposes. Because there was difficulty with funding all possible sites of enrollment, this registry reflects only a portion of the women who receive pregnancy care at Magee-Womens Hospital, but is generally reflective of the population as a whole. Any woman who received prenatal care at any of these sites was offered participation in the registry by signing an informed consent form. Institutional Review Board approval had previously been obtained for creation of the registry. The University of Pittsburgh Institutional Review Board declared the study to be exempt from protocol review. The Research Registry was cross-referenced with the hospital microbiology laboratory data with the use of unique patient identifier numbers in order to maintain subject anonymity. The cohort, after cross-matching with the microbiology database, included all registered pregnant women with GBS bacteriuria from February 2002 to June 2004. The control group was composed of subjects that were defined as the next pregnant woman in the registry in consecutive order of medical record number with a negative urine culture. Subjects were excluded from analysis if mistakenly enrolled more than once, if they had any urinary pathogen other than GBS, or if their urine collection was found not to be the first of their pregnancy.

Medical record charts were reviewed by two investigators. Demographic data were obtained, as were data pertaining to potential confounding variables. Demographic variables collected included age, race, insurance status, and parity. Associated risk factors were collected, including multiple gestation, cervical conization, and uterine anomalies. Information on sexually transmitted infections diagnosed during the prenatal period was collected, including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, or clinically evident

herpes simplex virus. Potential risk-modifying exposures were noted, including the self-reported use of tobacco or drugs.

The characteristics of the antepartum urine cultures were collected from the chart. The first urine collected from the clinic for each woman was recorded. The urine culture for each woman was recorded only once. In general, the method of collection used in the clinic is clean-catch midstream urine. Gestational age at the time of collection of urine was noted. The routine hospital laboratory protocol for urine cultures was used. Urines are plated on sheep blood agar, MacConkey agar, and GBS agar plates (Northeast Laboratory, Winslow, ME, USA). In order to determine the grouping of β -hemolytic colonies that do not grow on the GBS agar plates, a GBS-specific antisera latex agglutination method (Oxoid, Basingstoke, UK) is used. Each colony that grows on sheep or MacConkey agar is considered 1000 cfu/mL. If there are no colonies of GBS on these agars, then any growth on the GBS agar plate is considered less than 1000 cfu/mL. Treatment for bacteriuria was noted as recorded in the medical record, as was the particular agent used for treatment, if available.

Information regarding the use of antibiotics other than those for treatment of GBS bacteriuria was collected. The coding for this variable was considered positive if a subject received antepartum antibiotics for any reason. Antepartum status was defined as prior admission to the hospital for delivery of the index pregnancy. Details such as the type of antibiotic or the type of infection were not rigorously recorded but included other urinary tract infections, sexually transmitted infections, or upper respiratory infections.

Details regarding labor and delivery were recorded. These included clinical diagnoses of preterm labor or premature rupture of membranes. The requirement for tocolysis was noted, as was administration of betamethasone therapy. Delivery data were also recorded including gestational age at delivery, infant birth weight, Apgar scores, and admission to the neonatal intensive care unit. The primary outcome for this analysis was preterm birth defined as delivery at less than 37 weeks of gestation. Gestational age was determined by best obstetrical estimate, commonly the woman's last menstrual period and a second trimester ultrasound.

Continuous variables were assessed for normal distribution using the skewness and kurtosis test as well as a normal density histogram. Since most of the continuous variables were not normally distributed, transformation to approximate a normal distribution was attempted. Nonparametric analysis was performed to compare medians of continuous variables using the Kruskal-Wallis test when transformation to a normal distribution was not possible. Categorical variables were analyzed using Pearson χ^2 or Fisher exact test as appropriate. Multiple logistic regression analysis was performed to determine odds ratios. Potential confounding variables at the $P=0.1$ level were included in the final multivariable model. $P<0.05$ was considered significant. Statistical analyses were performed with Stata 9.0 (Stata Corporation, College Station, TX, USA).

3. Results

A total of 423 pregnant women were included, 220 in the negative urine culture group and 203 in the GBS bacteriuria group. Demographic characteristics are shown by group in Table 1. There were no significant differences between the groups with regard to most demographic factors. Women in the bacteriuria group had their urine collected at a slightly later median gestational age and had a higher prepregnancy body mass index. The median gestational age at delivery among the entire cohort was 39 weeks (range, 17–42 weeks). The frequency of preterm birth among the entire cohort was 18%.

Among the women with GBS bacteriuria, the median gestational age at delivery was significantly lower in the group who received additional antibiotics (38.8 vs 39.4 weeks;

$P=0.005$). Importantly, the women who received additional antibiotics were more likely to deliver preterm than those who did not receive additional antibiotics and those who were nonbacteriuric (Table 2). There were no statistically significant differences in other adverse outcomes related to exposure to additional antibiotics, such as preterm rupture of membranes, chorioamnionitis, or neonatal intensive care admission. After adjusting for potential confounding variables, among women with GBS bacteriuria the use of additional antibiotics was independently associated with an increased risk of preterm birth (adjusted odds ratio (aOR) 2.7, 95% CI, 1.2–6.1). The univariate and adjusted odds ratios of the variables included in the final multivariable model assessing associations with preterm birth are shown in Table 3. Diagnosis of sexually transmitted infections during the course of the pregnancy did not impact the findings in the model. We found no statistically significant difference in risk among women without GBS bacteriuria who received additional antibiotics (aOR 1.9, 95% CI, 0.82–4.2).

4. Discussion

The present study suggests that among women with GBS bacteriuria, the use of additional antibiotics beyond those given for treatment of the bacteriuria is associated with an increased risk of preterm birth prior to 37 weeks of gestation. This risk is present even after controlling for potential confounding variables, including treatment of the GBS bacteriuria and prior preterm birth. We were unable to demonstrate, however, the same significant association among women who did not have GBS bacteriuria; although the odds ratio was elevated, the confidence interval crossed 1.0. The lack of a significant association may have been related to inadequate sample size and β error.

The mechanism for the association between preterm birth and additional antibiotics is unclear. However, several investigations have found increased rates of preterm birth or no effect, rather than the expected decreases in trials of antibiotic use for the purpose of reduction of preterm birth [9,12,14,15]. There have been several theories suggested. Some have suggested that there could be a “killing” phenomenon that causes release of inflammatory substances from the organisms [18]. This might predispose to development of preterm labor or premature rupture of membranes. An alternative theory is that the increase in preterm birth may be related to alteration in vaginal flora. Carey and Klebanoff [19] performed a secondary analysis of data collected in the Vaginal Infections and Prematurity Study and showed that both exposure to metronidazole prior to 32 weeks of gestation and heavy growth of *Escherichia coli* or *Klebsiella pneumoniae* were associated with an increase in preterm birth among that cohort. This particular theory suggests that heavy growth of pathogenic organisms ascend into the upper genital tract and lead to preterm birth.

A strength of the present study is that we included a relatively large cohort of women, allowing for stratification of risk factors in the analysis. Additionally, the chart abstraction consisted of a large variable set such that the analysis controlled for many potential confounding variables. However, because this was a secondary analysis it was an incomplete assessment. One limitation was the inability to quantify the indication for additional antibiotics, as well as the type of antibiotic received. However, we did evaluate the diagnosis of various sexually transmitted infections during pregnancy and did not observe an effect on the odds of preterm birth in either univariate or multivariable analysis when these infections were included in the logistic regression model. Diagnosis of bacterial vaginosis or administration of antibiotics for bacterial vaginosis was not systematically collected in this cohort. It has been documented in several studies that bacterial vaginosis is associated with an increased risk of preterm birth [21,22]. Thus, we believe that the additional antibiotics could be a marker for increased risk of preterm birth due to somewhat minor infections. We are also unable to determine whether these antibiotics were prescribed for true bacterial infections. Another potential source for confounding is the GBS bacteriuria itself. While treatment of GBS bacteriuria has previously

been shown to decrease the risk of preterm birth associated with bacteriuria [10], it may not lower the risk for women who do not have GBS bacteriuria. In planning the analysis, we believed GBS to be an effect modifier because it is thought to be associated with both the exposure variable, antibiotics, and the outcome variable, preterm birth [23]. Among this cohort, however, we have not demonstrated a strong association between GBS bacteriuria and preterm birth. Given this fact and the extensive list of variables tested for inclusion in the logistic regression model, we believe that the independent association between additional antibiotics and preterm birth is valid, recognizing that there is potential bias which we cannot exclude. Finally, while we detected an increased risk of preterm birth at less than 37 weeks of gestation, we had an insufficient sample size to detect a small increase in risk of preterm birth at lower gestational ages. The study only had 38% power to detect such a difference with the available sample size.

Our analysis provides additional support for the notion that there may be adverse pregnancy effects from the use of antibiotics or from the infections that cause their use to be needed. Because of the retrospective nature of this analysis we are unable to make recommendations regarding the use of antibiotics among unselected patients in pregnancy. Prospective evaluation of vaginal flora before and after the use of antibiotics for specific pathogens may be helpful in discerning the effects of antibiotic use in pregnancy on normal flora.

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Table 1

Demographic characteristics of the groups

	GBS bacteriuria (n=203)	Negative culture (n=220)	<i>P</i> value
Maternal age, median (range)	25 (15–44)	26 (16–44)	0.2
African American race, n (%)	79 (39)	83 (38)	0.6
Parity, median (range)	1 (0–1)	1 (0–1)	0.9
Gestational week at urine collection, median (range)	12.9 (4–39)	9 (4–37)	<0.01 ^a
BMI, median (range)	24.3 (15–78)	22.9 (15–50)	<0.01 ^a
Tobacco use, n (%)	43 (21)	53 (24)	0.5
STIs, n (%)	30 (15)	33 (15)	0.7
Prior preterm birth <37 weeks, n (%)	24 (12)	26 (12)	0.9

Abbreviations: GBS; Group B streptococcus; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); STI, sexually transmitted infections, including *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis*, or clinically evident herpes simplex virus.

^aKruskal-Wallis comparison of medians.

Table 2
Frequency of outcome based on group of urine culture result and receipt of additional antibiotics

Outcome	Negative culture without additional antibiotics (n=156)	Negative culture with additional antibiotics (n=64)	P value ^a	GBS bacteriuria without additional antibiotics (n=120)	GBS bacteriuria with additional antibiotics (n=83)	P value ^a
Preterm delivery <37 weeks, n (%)	20 (13)	15 (23)	0.05	19 (16)	23 (28)	0.04
Preterm delivery <34 weeks, n (%)	7 (5)	7 (11)	0.12	5 (4)	7 (8)	0.24
PPROM, n (%)	5 (3)	6 (9)	0.08	3 (3)	7 (9)	0.09
Chorioamnionitis, n (%)	9 (6)	8 (13)	0.1	16 (13)	19 (23)	0.09
NICU admission, n (%)	6 (4)	7 (11)	0.06	13 (11)	11 (13)	0.66

Abbreviations: GBS, Group B streptococcal; PPRM, preterm premature rupture of membranes; NICU: Neonatal Intensive Care Unit.

^aFisher exact test

Table 3

Univariate and multiple logistic regression of association of risk of preterm birth with additional antibiotics among women with GBS bacteriuria

Variable	Univariate OR (95% CI)	Adjusted OR (95% CI)
Additional antibiotics	2.1 (1.0–4.4) ^a	2.7 (1.2–6.1) ^a
Prior preterm birth	3.8 (1.5–9.7) ^a	3.9 (1.5–10.5) ^a
Treatment of GBS bacteriuria	0.8 (0.4–1.7)	0.51 (0.22–1.2)
Gestational age at urine collection	0.99 (0.96–1.02)	0.97 (0.93–1.0)
BMI < 18	1.99 (0.49–8.1)	2.78 (0.61–12.7)

Abbreviations: GBS, Group B streptococcal; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); OR, odds ratio.

^aIndicates $P < 0.05$.