Longitudinal Investigation of Candida Vaginitis in Pregnancy: Role of Superimposed Antibiotic Use

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Objective: To evaluate the purported association of antibiotic use and subsequent symptomatic Candida vaginitis among pregnant women.

Methods: Two hundred fifty obstetric patients were followed in a prospective, culture-based, longitudinal, and observational study from the first antepartum appointment through the postpartum visit at 6 weeks. All patients were cultured for yeast (Nickerson agar) initially. Patients with symptoms and microscopic evidence of vaginitis at the initial visit were followed through pregnancy but were not analyzed with asymptomatic individuals who had vaginal cultures for Candida at the first visit and at subsequent visits if they developed vulvovaginal symptoms. Patients were categorized as colonized or uncolonized on the basis of initial cultures and were evaluated at least monthly for antibiotic use and vaginal complaints. In addition, hospital records were reviewed after the final visit to document antibiotic use or vaginal infection.

Results: Asymptomatically colonized patients were at a threefold greater risk of developing symptoms than were uncolonized patients \((P < .001)\). Among women receiving antibiotics during pregnancy, 61% developed symptoms of Candida vaginitis compared with 15.6% of women who did not receive antibiotics. For the entire study population, 46% of the patients received at least one course of antibiotic therapy and 21% had multiple courses. Only three of the seven who became symptomatic with yeast vaginitis did so within 4 weeks of treatment. Many of the antibiotic regimens were prescribed by providers other than the obstetrician.

Conclusion: Antibiotic treatment during pregnancy was frequent in the study population, but it was not associated with a significant risk of developing Candida vaginitis. (Obstet Gynecol 1998;91:115–8. © 1998 by The American College of Obstetricians and Gynecologists.)

Among reported associations in the medical literature is the increased risk of vulvovaginal candidiasis after antibiotic treatment. This tenet may have originated from observations involving antibiotics in use decades ago or from previously employed treatment regimens.

To determine whether antibiotic therapy is associated with an increased risk of vaginal candidiasis, we documented the development of yeast vaginitis symptoms after antibiotic use among pregnant patients. The data provide information only about the association between antibiotic therapy and vaginal candidiasis in pregnant women; no inference can be made regarding the role of antibiotics in vaginitis among nonpregnant women. Because pregnancy is associated with a heightened propensity to yeast vaginitis, and pregnant women are followed closely throughout gestation, this population may provide an indicator of an antibiotic-yeast association.

Materials and Methods

All patients initiating obstetric care at the four rural obstetric outreach clinics of the Robert C. Byrd Health Sciences Center of West Virginia University were eligible initially for inclusion in the study. Women enrolled in this study were followed by an author throughout the duration of their pregnancies. Two hundred fifty patients entered the study sequentially over a period of 12 months after consenting to a protocol approved by the West Virginia University Institutional Review Board for the Protection of Human Research Subjects.

Participants were entered at the time of their first antepartum visit, with a mean gestational age of 13.1 weeks. Inclusion criteria included the first vaginal examination in the current gestation and a medical indication for a speculum examination. At that visit, a Venereal Disease Research Laboratory test, cervical culture for Neisseria gonorrhoeae, direct immunofluorescent antibody test for Chlamydia, and Papanicolaou tests were performed. A human immunodeficiency virus
(HIV) test was offered. Vaginal culture for *Candida albicans* was inoculated onto Nickerson agar, incubated for 48–72 hours at room temperature, and observed for the appearance of characteristic brown colonies. These patients also had a speculum examination to evaluate for evidence of vaginitis. Individuals with symptomatic lower genital infection due to any cause (six vulvovaginal candidiasis, two *Trichomonas* vaginitis, and one with bacterial vaginosis) were evaluated throughout pregnancy, but they were not analyzed with the 250 patients who form the basis for this investigation. To follow patients longitudinally, it was necessary for participants to have more than one visit. In all, 24 patients enrolled initially could not be followed (13 had early obstetric loss, four moved from the area, three were referred to the high-risk clinic, two were found on review of the family physician’s records to have been treated in early pregnancy for yeast vaginitis, one culture was lost, and one patient’s history was not credible).

All patients were evaluated at least monthly for signs and symptoms of vulvovaginal candidiasis and again at 6 weeks postpartum. At each visit, patients were asked about symptoms such as itching, burning, painful intercourse, painful urination, rash, or redness on the vulva or perineum. Patients with one or more symptoms received a follow-up culture and were evaluated for quantity and character of the vaginal discharge. At each visit, despite vaginitis status, each patient was asked about antibiotic use. Enquiry was made specifically regarding topical, parenteral, and oral antimicrobial agents. Patients were asked to provide the prescription container for examination.

Patients were included if they had at least one additional visit in which antibiotic use and vaginitis symptoms could be determined after their initial enrollment. For any patient who developed one or more symptoms consistent with yeast vaginitis, examination and culture were performed, and wet mounts were obtained. Those who had corroborating physical signs and laboratory findings were classified as having become symptomatic. Treatment by other physicians or self-treatment without verification of the diagnosis also was classified as symptomatic yeast vaginitis. The obstetric clinics were collocated with rural family practice clinics, permitting access to the family medicine records that were reviewed for the patients in this study. In addition, all of each patient’s hospital records were reviewed after hospital discharge for antibiotic use during the pregnancy and for documented yeast vaginitis. Chi-square analysis for 2 × 2 contingency tables was used for statistical evaluation when appropriate, with *P* < .05 considered significant.

### Table 1. Characteristics of Antimicrobial Treatment and Circumstances of Use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic treatment events</td>
<td>231</td>
</tr>
<tr>
<td>during pregnancy*</td>
<td></td>
</tr>
<tr>
<td>Distribution by trimester of treatment events</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>40 (17.3%)</td>
</tr>
<tr>
<td>II</td>
<td>65 (28.1%)</td>
</tr>
<tr>
<td>III</td>
<td>126 (54.5%)</td>
</tr>
<tr>
<td>Drugs most frequently prescribed</td>
<td></td>
</tr>
<tr>
<td>Penicillins</td>
<td>63 patients, 74 courses</td>
</tr>
<tr>
<td>Macrolides</td>
<td>51 patients, 69 courses</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>22 patients, 23 courses</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>22 patients, 24 courses</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>13 patients, 13 courses</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>8 patients, 8 courses</td>
</tr>
</tbody>
</table>

*Excludes those treated for vulvovaginal candidiasis symptoms developing during the period of observation. One patient may have been treated on more than one occasion during pregnancy.

### Results

All patients enrolled in this study were asymptomatic initially and were categorized as colonized (52 patients) or uncolonized (198 patients) at the time of their initial visit. Colonized individuals were followed for an average of 28.2 (± 11.7 standard deviation [SD]) weeks, and uncolonized patients were followed for an average of 30.8 (± 10 SD) weeks. During observation, 13 of 52 (25%) colonized patients became symptomatic with yeast vulvovaginitis, whereas 15 of 198 (7.6%) (*P* = .004) uncolonized patients developed symptoms. Thus, the relative risk of symptomatic vulvovaginal candidiasis developing in association with vaginal colonization was 3.30 (confidence interval [CI] = 95%), which was statistically significant *P* < .001.

Before analyzing data on yeast vaginitis, we characterized the antibiotic use pattern in the entire patient cohort. Of the 250 patients completing this study, 115 (46%) received an antibiotic at some time during pregnancy. Some patients received more than one course of therapy, resulting in 231 antibiotic-use events. Extreme cases included one patient treated for 85 days with β-lactam medications and several patients who required four courses of antibiotic treatment during their pregnancies. Table 1 provides a summary of the major features of antibiotic use among all enrolled patients. Many patients are long-term cigarette smokers, which may account for some excess antibiotic use to treat bronchitis. Interestingly, many antibiotic treatment events were undertaken without obstetric consultation. Approximately 40% of antibiotic prescriptions were provided by emergency and family medicine physicians. Six patients were admitted to the surgical service during pregnancy, accounting for prescription antibiotic treatment by general surgeons.
Table 2. Relationship of Antibiotic Treatment During Pregnancy to Development of Yeast Vaginitis Symptoms

<table>
<thead>
<tr>
<th>Antibiotics administered during pregnancy</th>
<th>Became symptomatic</th>
<th>Remained asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initially colonized</td>
<td>Initially uncolonized</td>
</tr>
<tr>
<td>No</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

To determine if antibiotic use had an effect on a patient’s likelihood of developing symptoms of yeast vaginitis, the rate of symptom development, both in the whole population and in the colonized patients (Table 2), was calculated. The study initially evaluated all patients despite colonization status, because undetected asymptomatic colonization might precede subsequent development of symptoms. Among all patients, 11.2% became symptomatic despite antibiotic treatment. When the population was divided between those who had and those who had not received antibiotics during their pregnancy, those receiving antibiotics had a lower rate (6.1%) of symptom development than those not receiving antibiotics (15.6%). To the extent that these two groups are similar to random samples from obstetric populations, the relative risk of becoming symptomatic during pregnancies in which antibiotics were given compared with during pregnancies in which no antibiotics were given was 0.43 (95% CI: 0.19, 0.98), P = 0.035.

The study also determined whether this apparent protective effect of antibiotics also was seen in the asymptptomatically colonized patients, who were known to have a greater likelihood of developing symptomatic yeast infection. Of the colonized patients who received antibiotics, 15.6% became symptomatic, whereas 40% of those not treated with antibiotics developed symptomatic. To the extent that these two groups are similar to random samples from an obstetric population, there appeared to be a lower risk (.39 relative risk, 95% CI = .15, 1.03) of becoming symptomatic with antibiotic treatment. Uncorrected \(\chi^2\) analysis yielded \(P = .048\), but with the more conservative estimate using the Yates correction, \(P = .099\).

From these data, antibiotics apparently did not predispose to yeast vaginitis symptoms in the study population. Nevertheless, there were several patients who did develop symptoms after antibiotic treatment. If the antibiotics were affecting the development of symptomatic vaginal candidiasis, such antibiotic use may be expected to occur at a time close to the genesis of symptoms. Only three of the seven women who developed symptoms after antibiotic treatment did so within 4 weeks of antibiotic therapy. The remaining four became symptomatic as late as 113 days after completion of antibiotic therapy.

Although antibiotics did not appear to predispose to yeast vaginitis, specific classes of antibiotics might have promoted symptomatic mycotic infection. However, the data failed to reveal any relationship between a specific class of antibiotic and development of yeast vaginitis symptoms. Symptomatic yeast vaginitis developed among none of the 52 patients who received nitrofurantoin, sulphonamides, or cephalosporins; only one of the 51 patients who received macrolide antibiotics; and five of the 63 receiving oral penicillins. Nevertheless, the vast majority of antibiotics in use today contain statements on the drug package inserts listing yeast vaginitis as a possible adverse reaction.

The authors examined several characteristics in the database to determine if there were confounding variables that distinguished the antibiotic-treated group from the untreated group. Patients who received antibiotics during pregnancy were observed for an average of 31 weeks ± 10 weeks (SD), compared with 29.6 weeks ± 10.7 weeks (SD) for the untreated patients. Obesity was indicated by a body mass index (BMI) of greater than 27. Among antibiotic-treated women, 55.5% were obese (mean BMI = 28.77 ± 6.95 SD), and 34.4% of non-antibiotic-treated women (mean BMI = 25.8 ± 6.12 SD) were obese at the enrollment visit. There were nine diabetic patients in the study, three of whom were in the antibiotic-treated group. None of these factors appeared to account for the differences seen between antibiotic-treated and non-treated patients.

Finally, among the patients studied, 15 had extensive exposure to antibiotic compounds, defined here as at least three courses of antibiotic therapy, most lasting for a total of more than two weeks. The results from these patients provide additional evidence that extensive antibiotic therapy with the drugs listed appears to pose little risk for development of yeast vaginitis.

Discussion

Almost all gynecology or internal medicine textbooks contain the statement that Candida vaginitis may arise because of antibiotic treatment. Tetracycline is mentioned often as the entity most likely to be responsible. The presumed association of antibiotics and vaginitis may have derived from experiences with antibiotic-prescribing practices of an earlier time, although a recent study among HIV-infected patients found antibiotics to be risk factors for yeast infection in the postpartum but not antepartum period.

Caruso provided evidence that supported the concept of an effect of antibiotics on yeast infection in a culture-based study involving oral tetracycline phosphate administered to three groups of subjects for 7, 14,
or 21 days. The rate of positive culture increased from 7% before the study to 10%, 11%, and 24% for the groups treated for 7, 14, and 21 days, respectively. Caruso examined the rate of positive culture as his endpoint, although none of the 59 patients did develop at least one symptom associated with vaginal infection. Whereas data from this study confirm that colonization is a risk factor for subsequent symptomatic candidiasis, one must be careful in asserting that increased prevalence of colonization is identical to increased rates of symptomatic disease.

The concept that antibacterial drugs may predispose to yeast vaginitis has a sound theoretic basis. Many investigators believe that the fungal and bacterial populations of any colonized tissue are in reciprocal balance. Savage and Dubos found that in the mouse stomach, part of the gastric epithelium was colonized by lactobacilli in almost pure culture, and a separate portion of the stomach was colonized by yeast. If an antibiotic was used to eliminate the Lactobacillus, the yeast colonization spread to the entirety of the gastric epithelium. However, the relationship of yeast and bacteria may not be the same in the vagina, where the two types of organisms are not segregated spatially. In working with a rat model of Candida colonization, Larsen and Galask found that rats were naturally resistant to yeast colonization unless they were estrogenized. Bacteriologic studies showed that estrogen priming also increased bacterial colonization of the vagina by several orders of magnitude, suggesting that the bacterial and yeast populations may not exhibit an inverse relationship, at least in this system. Human studies have implied that yeast and Lactobacillus are together supported by an estrogenized epithelium.

Pregnancy served as a means to allow longitudinal investigation of development of vaginitis symptoms, because patients seeking routine gynecologic care would be unlikely to devote the time to repeated follow-up visits. Yeast infection often is superimposed on a background of pregnancy, thus, the study population was a potentially more sensitive indicator of the putative effect of antibiotics on development of symptomatic vulvovaginal candidiasis, although candidiasis in pregnancy may or may not resemble candidiasis in nonpregnant patients. The authors were surprised to find that non-antibiotic-treated patients actually became symptomatic more frequently than did the patients treated with antibiotics, and they were unable to demonstrate that any particular antibiotic showed a propensity to elicit vaginal symptoms. Vulvovaginal candidiasis was rare among the patients who received intensive antibiotic therapy who were evaluated.

The mechanism involved in these unexpected findings is unknown, but the possibility that antibiotics could increase yeast colonization, as reported by Caruso, without necessarily causing symptoms, cannot be ruled out. A study would be needed to verify that possibility specifically. Conspicuously absent from the antibiotics used in our population was tetracycline, which is mentioned commonly in association with vaginitis, reflecting an awareness among obstetricians and nonobstetricians alike of the potential for drug-induced harm to the fetus.

This study elicited another unexpected finding. The rate of antibiotic use among pregnant patients (46%) was greater than anticipated, because most individuals providing care for pregnant patients limit drug use to compelling clinical situations. An estimated 40% of the antibiotic prescriptions were written by emergency and family medicine physicians. Dentists are faulted commonly for prescribing antibiotics that are not reported to the patient's obstetrician. However, in our study, little antibiotic use could be attributed to dental practitioners.

Overall, the present study is reassuring concerning the likelihood that antibiotic therapy places an additional burden of vulvovaginal candidiasis on pregnant patients beyond that normally associated with pregnancy.

References

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Received June 2, 1997.
Received in revised form August 26, 1997.
Accepted September 11, 1997.

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