Cervical Inflammation And Preterm Delivery In Pregnant Women With A History Of Preterm Delivery

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Background: A previous preterm delivery is a risk factor for preterm delivery in a subsequent pregnancy. We tested the hypothesis that evidence of inflammation on a Papanicolaou smear obtained during pregnancy is a risk factor for preterm delivery for women with a history of preterm delivery.

Methods: We studied women who had two singleton deliveries at a university hospital during an 8-year period. Women eligible for our study were those whose first delivery was preterm (<37 weeks of gestation) and for whom a Papanicolaou smear was obtained during the second pregnancy. These smears were examined for evidence of inflammation by a cytopathologist. Information about the second pregnancy was obtained by chart review.

Results: The cytopathologist reviewed Papanicolaou smears from 92 study pregnancies and found evidence of cervical inflammation on 34 smears (37 percent). Preterm delivery ended 24 (26.1 percent) of the second pregnancies. The incidence of preterm delivery in women with inflammation on Papanicolaou smear was 41.2 percent compared with an incidence of 17.2 percent in women without inflammation (relative risk of 2.40 with a 95 percent confidence interval of 1.19 to 4.83). This association remained significant after controlling for potential confounding variables. A stratified analysis found that the association of cervical inflammation with preterm delivery was limited to women who had systemic exposure to an antibiotic during pregnancy.

Conclusion: Among pregnant women with a history of preterm delivery, evidence of inflammation on Papanicolaou smear was associated with an increased risk of preterm delivery. If replicated in other studies, this finding might have implications for the management of pregnancies in women with a history of preterm delivery. (J Am Board Fam Pract 1994; 7:465-71.)

Delivery before 37 completed weeks of gestation is a major cause of neonatal morbidity and mortality. During the 1980s in the United States, the percentage of births that were preterm increased.[1] Most preterm deliveries result from the preterm spontaneous onset of labor; despite considerable investigation, the etiology and pathogenesis of preterm labor are incompletely understood.[2] There is evidence that in some cases preterm labor is causally related to cervicovaginal infection.[3-9]

A previous study of deliveries at the University of Missouri–Columbia Hospital and Clinics explored the possible association of preterm labor and delivery with cervical inflammation detected by cytological screening of pregnant women.[10] Evidence of inflammation on Papanicolaou

smears was not a risk factor for preterm labor or preterm delivery in this sample of 577 pregnant women. Subgroup analyses suggested, however, that cervical inflammation was a risk factor among the 38 women with a history of preterm labor or preterm delivery. The current study was conducted to explore the hypothesis generated by the previous study that cervical inflammation evident on Papanicolaou smear is associated with an increased risk of preterm delivery in pregnant women with a history of preterm delivery.

Methods

The study sample consisted of women who had two deliveries at the University of Missouri Hospital and Clinics in Columbia, Missouri, between 1 January 1984 and 31 December 1991. Women were eligible for the study if they met the following criteria: (1) they gave birth to a singleton infant prior to 37 weeks' gestation (preterm delivery) between 1 January 1984 and 31 December 1990 (the qualifying pregnancy), (2) their delivery was preceded by spontaneous preterm labor, (3) they subsequently gave birth to a singleton infant at the hospital during the period 1 January

1985 and 31 December 1991 (the study pregnancy), and (4) they had a Papanicolaou smear obtained during the second pregnancy and interpreted in the hospital cytopathology laboratory. Obstetric care was provided by either obstetricians or family physicians on the attending staff or residency staff of the hospital.

Data were collected from patient hospital records by one reviewer, a first-year medical student (SD), who received special training to recognize relevant information in the charts. Using uniform definitions and criteria, the reviewer abstracted chart data onto a coding sheet that was specially developed for this study. The following information pertaining to the study pregnancy was collected for each patient: demographic factors, behavioral and lifestyle characteristics, obstetric history, certain events occurring during pregnancy, and pregnancy outcomes. In addition, the hospital records were reviewed to document the preceding preterm delivery (the qualifying pregnancy) and to establish that this delivery resulted from preterm labor. Information about 32 separate variables was collected from each chart. To assess measurement reliability, 15 randomly selected patient charts (16.3 percent of the sample) were reviewed independently by another investigator (RLB). The rate of agreement of the two reviewers across all 32 variables was 96.7 percent, and there was 100 percent agreement for the major outcome variable, presence or absence of preterm delivery. In addition, after the analysis of data, a supplemental review of selected charts was conducted by RLB to determine indications for antibiotic treatment.

The presence or absence of cervical inflammation (the exposure variable) was determined by the examination of each Papanicolaou smear slide by a cytopathologist (EI) who was unaware of the outcome of the study pregnancy or the original laboratory findings. During the 8-year study period, cervical specimens for cytologic examination were obtained from pregnant women using a cotton swab or an extended-tip wooden spatula. In the absence of widely accepted explicit criteria for the presence of inflammation on Papanicolaou smear, the cytopathologist developed a scoring system based on his experiences and reports in the literature.[11-15] Table 1 shows the scoring system; in this system evidence of inflammation is based on the presence of leukocytes only and is

Table 1. Criteria for Assessing Inflammation on Papanicolaou Smear.*

Score	Description
0	No leukocytes present
1	Leukocytes only in mucus
2	Minimal leukocytes, diffusely distributed, non-obscuring
3	Diffuse leukocytes, focally obscuring epithelial cells
4	Diffuse leukocytes, obscuring 50 percent to 75 percent of epithelial cells
5	Extensive leukocytes, obscuring >75 percent of epithelial cells, precluding satisfactory evaluation

*For the purpose of the analysis, scores of 3 and higher were used to indicate the presence of inflammation.

not dependent on cellular atypia or other cytopathologic findings. In the data analysis, the exposure variable was dichotomous: a score of 3 or higher denoted the presence of inflammation, and a score of less than 3 indicated the absence of inflammation. This cut point was established before the assessment of outcomes.

The cytopathology laboratory report for each Papanicolaou smear was reviewed by the chart auditor, who noted the presence or absence of a finding of inflammation. No explicit criteria were used by the laboratory to assess Papanicolaou smears for evidence of inflammation. A notation that inflammation was present was based on the judgment of the cytopathology staff regarding the quantity of leukocytes in the smear. The examination of each smear by the cytopathologist for the purpose of this study was conducted without knowledge of the official laboratory interpretation. For 78.3 percent of the study smears, there was agreement between the independent review by the cytopathologist and the laboratory report regarding the presence or absence of inflammation. The Cohen kappa statistic[16] was 0.53, indicating a moderate level of interobserver concordance.

Measurement of the primary outcome variable was based on the gestational age at the time of delivery. Women who were delivered before 37 completed weeks of gestation were considered to have had a preterm delivery. For nearly all patients, one or more sonograms obtained during pregnancy contributed to the assignment of gestational age. We also analyzed the data with delivery by 33 weeks of gestation as the outcome.

Data were processed and analyzed using SPSS-PC Version 4.0.[17] Differences involving categorical variables were assessed with the chi-square statistic or the Fisher exact test. Differences between means were assessed statistically with analysis of variance. The possible association of cervical inflammation with an outcome was quantified by calculating a relative risk, the ratio of the incidence of the outcome in women with cervical inflammation to the incidence in women without cervical inflammation. The test-based method[18] was used to calculate 95 percent confidence limits to the point estimate of relative risk. Logistic regression analyses controlled for possible confounding by variables that were associated with the exposure and the major outcome on univariate analysis. Adjusted odds ratios were calculated by exponentiating regression coefficients, and 95 percent confidence limits were calculated. Stratified analyses explored the association of the exposure with the major outcome for women with and without antibiotic treatment and for women with and without urinary tract infection.

Results

One hundred study pregnancies met eligibility criteria for the study; Papanicolaou smears obtained for 92 of them were available for blinded review by the cytopathologist. Based on his examination of these slides, 34 (37 percent) women were considered to have cervical inflammation, and 58 (63 percent) were considered to have no cervical inflammation. Table 2 shows a comparison of these two groups with respect to various demographic, social, behavioral, and obstetric characteristics. Except for the rates of antibiotic use and hypertension, which tended to be higher in women with inflammation, these groups were similar with respect to the distribution of these characteristics. Two or fewer women in the sample had hydramnios, pyelonephritis, or recorded use of an illegal drug.

Of the 92 study pregnancies, 24 (26.1 percent) ended in a preterm delivery. The rate of preterm delivery in women with evidence of inflammation on Papanicolaou smear was significantly higher than the rate for women without inflammation (41.2 percent versus 17.2 percent, $P=0.013$). The relative risk (RR) of preterm delivery in women with inflammation compared with women without inflammation was 2.40 with a 95 percent con-

Table 2. Comparison of Study Groups by Demographic, Social, Behavioral, and Obstetric Characteristics.

Characteristic	Inflammation		
	Present (n=34)	Absent (n=58)	P Value
	Means		
Maternal age at delivery (years)	23.6	24.2	0.52
Gravidity	3.3	3.3	0.91
Parity	1.6	1.8	0.39
Education (years)	11.6	11.6	0.83
	Percentages		
White	71	66	0.62
Married	62	57	0.65
Payment: Self-pay	18	21	
Medicaid	54	45	0.70
Insurance	27	34	
Cigarette smoker	36	47	0.34
Alcohol use	9	12	0.64
Cervical gonococcal test positive*	3	4	0.89
Cervical chlamydia test positive[†]	4	6	0.78
Systemic antibiotic treatment[‡]	65	48	0.13
Hypertension	15	5	0.12
Diabetes mellitus[§]	15	10	0.53
Urinary tract infection[‖]	32	29	0.76
Vaginal delivery	71	67	0.74

*Cervical specimens were obtained from 30 women with inflammation and 51 women without inflammation and cultured on Thayer-Martin agar. Denominators are 30 and 51.
[†]Chlamydiazyme test was performed on cervical specimens from 25 women with inflammation and 36 women without inflammation. Denominators are 25 and 35.
[‡]Antibiotics administered either orally or parenterally before onset of labor. Does not include intravaginal preparations.
[§]Includes gestational diabetes.
[‖]Women were considered to have a urinary tract infection if they received systemic antibiotic treatment for one or more of the following: urinary symptoms, abnormal urinalysis or urine dipstick test, and positive urine culture.

fidence interval (CI) of 1.19 to 4.83. The only other measured variable that was significantly associated with preterm delivery was hypertension occurring during pregnancy. The rate of preterm delivery in women with hypertension was 62.5 percent compared with a rate of 22.6 percent in women without hypertension ($P=0.01$). There were trends in the direction of higher rates of preterm delivery in women with a positive cervical gonococcal culture ($P=0.12$), in women with a positive cervical chlamydia test ($P=0.12$), and in women who received systemic antibiotics ($P=0.16$).

Preterm premature rupture of membranes occurred in seven pregnancies, all of which ended with preterm delivery. Incidence rates of preterm premature rupture of membranes were 14.7 percent for women with cervical inflammation and 3.4 percent for women without inflammation ($P=0.10$).

Women with cervical inflammation were five times more likely than women without inflammation to give birth at or before 33 weeks of gestation (17.6 versus 3.4 percent, $P=0.02$). The mean gestational age at delivery was significantly lower for women with inflammation (36.3 weeks versus 38.0 weeks, $P=0.008$), and birth weight tended to be lower in infants of women with inflammation (2761 g versus 3031 g, $P=0.07$).

To control for potential confounding by other variables, logistic regression analyses were performed. The association of cervical inflammation with preterm delivery remained statistically significant after adjusting for the effects of hypertension and systemic antibiotic use during pregnancy. In addition, the association persisted when the analysis was repeated after excluding women who had either a positive cervical culture for gonococcus or a positive chlamydia test.

Table 3 shows results of stratified analyses performed to assess possible modification of the apparent relation of cervical inflammation with preterm delivery by two variables, systemic antibiotic treatment and urinary tract infection. Fifty women received at least one antibiotic during pregnancy; 32 were treated with amoxicillin or ampicillin, 19 received metronidazole, 17 received erythromycin, and 12 received other antibiotics. Among these women, the presence of cervical inflammation on Papanicolaou smear was a risk factor for preterm delivery ($P=0.003$). In contrast, there was no association of inflammation with preterm delivery among women who did not receive antibiotic treatment.

The most common indication for antibiotic treatment was a urinary tract infection; 28 women received an antibiotic for one or more presumed urinary tract infections. Diagnostic criteria for urinary tract infection were variable and included the presence of urinary symptoms or an abnormal urinalysis only. Among the 28 women who had one or more urinary tract infections diagnosed during pregnancy, cervical inflammation conferred a significantly increased risk of preterm delivery ($P=0.004$). Treatment of all but one of these women included amoxicillin or ampicillin, which in most cases was the only treatment. Among the 32 women treated with amoxicillin or ampicillin, there was a strong association of cervical inflammation with preterm delivery ($P=0.002$, data not shown). For the 22 women who were not considered to have a urinary tract infection but who received antibiotic treatment for some other reason, the association of inflammation with preterm delivery was not statistically significant ($P=0.17$). With the small subgroup size, however, the statistical power is low.

To explore the interaction between cervical inflammation and antibiotic treatment found in the stratified analysis, selected charts were reviewed by one author (RLB) to determine reasons antibiotics were prescribed. In this post-hoc collection of data, charts of women who received antibiotics were reviewed, unless the only antibiotic treatment consisted of amoxicillin or ampicillin used for a urinary tract infection. Charts of 30 women were reviewed, including all women who received metronidazole, erythromycin, multiple antibiotics, and amoxicillin or ampicillin for conditions other than urinary tract infections. This supplemental chart review found that 22 women re-

Table 3. Association of Cervical Inflammation with Preterm Delivery after Stratification by Antibiotic Treatment and Urinary Tract Infection.

Variable	Incidence of Preterm Delivery (%)		P Value	Relative Risk
	Inflammation Present	Inflammation Absent		
Antibiotic treatment*				
Yes (n=50)	54.5	14.3	0.003	3.81
No (n=42)	16.7	20.0	0.80	0.84
Urinary tract infection†				
Yes (n=28)	63.6	11.8	0.004	5.39
No (n=64)	30.4	19.5	0.32	1.56
Antibiotic treatment without urinary tract infection (n=22)	45.5	18.2	0.17	2.50

*Antibiotics administered either orally or parenterally before onset of labor.
†Women were considered to have a urinary tract infection if they received systemic antibiotic treatment for one or more of the following: urinary symptoms, abnormal urinalysis or urine dipstick test, and positive urine culture.

ceived systemic antibiotic treatment for vaginal discharge or other vaginal symptoms with or without abnormal findings on microscopic examination, 19 received metronidazole, and 10 received erythromycin for this indication. Women with cervical inflammation were somewhat more likely to receive antibiotic treatment for vaginal symptoms than were women without inflammation (P=0.15). Women who received treatment for vaginal symptoms were somewhat more likely than those without such treatment to deliver preterm (P=0.21). Among the 22 women treated for vaginal symptoms, 45.5 percent of those with cervical inflammation were delivered preterm compared with 27.3 percent of those without inflammation (P=0.38). In these analyses the small subgroup sizes limit statistical power. Among the 70 women who did not receive antibiotic treatment for vaginal symptoms, cervical inflammation was associated with preterm delivery (P=0.02).

Eleven women in this study were also subjects in a study by Blake, et al.[10] Although the methods of assessing cervical inflammation differed in the studies, the inclusion of these 11 women in the current analyses might not constitute a completely independent test of the hypothesis. After excluding these 11 subjects from the analysis, the rate of preterm delivery was 39.3 percent for women with inflammation compared with 18.9 percent for women without inflammation (RR=2.08, 95 percent CI of 1.02 to 4.33). The results of the logistic regression analyses and stratified analyses in this reduced sample of 81 subjects were very similar to those in the sample of 92.

Discussion
In this study of women with a history of preterm delivery, cervical inflammation evident on Papanicolaou smear obtained during a subsequent pregnancy was a risk factor for preterm delivery. Approximately 4 of 10 women with cervical inflammation were delivered before 37 weeks' gestation, and 2 of 10 were delivered by 33 weeks' gestation. The association of inflammation with preterm delivery persisted after controlling for potential confounding variables and after the exclusion of women who were subjects in the hypothesis-generating study.

The association of cervical inflammation with preterm delivery was particularly strong in women who were treated for a presumed urinary tract infection during the pregnancy. Almost 2 of 3 women with cervical inflammation who were considered to have a urinary tract infection were delivered preterm compared with 1 of 5 who had neither. Urinary tract infections were not diagnosed more frequently in women with cervical inflammation, nor was this diagnosis related to preterm delivery in this sample. The question of whether cervical inflammation increased the risk of preterm delivery for women who were not considered to have a urinary tract infection was not answered in this study; the 56 percent higher rate of preterm delivery in women with inflammation was not statistically significant. The statistical power to detect a meaningful effect, however, was limited.

There was also an apparent interaction between cervical inflammation and antibiotic treatment. At least part of this interaction reflected the strong concordance between antibiotic treatment and a diagnosis of urinary tract infection. Analyses to detect an interactive effect of antibiotic exposure independent of urinary tract infection were limited by small subgroups. After urinary tract infection, vaginitis was the most common indication for antibiotic treatment. The association of cervical inflammation with preterm delivery for women treated for vaginitis was not significant. Similarly, a relative risk of 2.5 among women with antibiotic treatment and no urinary tract infection was not statistically significant (Table 3). The possibility remains that antibiotic exposure was a proxy for one or more conditions other than urinary tract infection that enhanced the association of cervical inflammation with preterm delivery. A prospective study is needed to document clearly the occurrence of urinary and vaginal infection and other indications for antibiotic treatment.

The clinical logic underlying this study is based on two assumptions: cervicovaginal infection is causally related to some cases of preterm delivery, and inflammation evident on Papanicolaou smear reflects cervicovaginal infection. While not conclusive, there is considerable evidence supporting the first assumption.[3-9] The second assumption, however, is somewhat problematic.

We are not aware of any study that has explored in pregnant women a possible relation between infection and cervical inflammation detected on

Papanicolaou smear. Several studies have examined this relation in nonpregnant women, with inconsistent findings. Wilson, et al.[19] studied 102 women from three British general practices and a family planning clinic who had cervical inflammation found on cytologic examination. At least one cervical or vaginal pathogen was found in 75 percent of the women; however, this study lacked a control group. A study of women attending a sexually transmitted disease clinic found associations between inflammation evident on Papanicolaou smear and infection with *Chlamydia trachomatis* and *Trichomonas vaginalis*.[11] A study of women with inflammation on class I Papanicolaou smears found that 28.3 percent had evidence of human papillomavirus infection on colposcopy and biopsy.[12] Bertolino, et al.[20] studied asymptomatic women who had routine cytological screening in two primary care settings. While the recovery of chlamydia and *Trichomonas* organisms was higher in women with inflammation on Papanicolaou smear than those without inflammation, 71.4 percent of the women with inflammation had no pathogen found, a rate that was not significantly different from the comparison group. The clinical significance of evidence of inflammation on Papanicolaou smears of nonpregnant women remains uncertain.

The cause of cervical inflammation detected by cytologic screening in the pregnant women we studied is unclear. Eighty-eight percent of the women were tested for cervical gonorrhea and 66 percent were tested for cervical chlamydia during the study pregnancies. The rates of recovery of these organisms were the same in women with inflammation as in women without inflammation. Very few women underwent testing for the presence of other cervical or vaginal pathogens. Although the differences were not statistically significant, women with cervical inflammation were somewhat more likely than those without inflammation to receive systemic antibiotic treatment in general and specifically to receive treatment for vaginal symptoms. Thus, the assumption that cervical inflammation is a marker for cervicovaginal infection remains tentative.

This study found no evidence that antibiotic treatment during pregnancy reduced the risk conferred by cervical inflammation. In fact, the association of inflammation with preterm delivery was limited to the women who received systemic anti-biotics. It should be emphasized, however, that this retrospective study was not designed to assess the effect of antibiotic use; inferences regarding this issue are not warranted. Although it is conceivable that antibiotic exposure had a direct adverse effect, it is much more likely that this exposure was a marker for one or more conditions that modified the relation of cervical inflammation with preterm delivery. Elucidation of this apparent interaction and evaluation of the effects of antibiotic use on cervical inflammation await additional research.

In contrast to the study by Blake, et al.,[10] the assessment of evidence of inflammation on smears in this study was based on explicit criteria applied by an expert cytopathologist. In the previous study the exposure variable was based on the report from the hospital cytopathology laboratory; the cytopathology staff did not apply explicit criteria for the presence of inflammation. For the smears examined in the current study, there was moderate agreement (kappa = 0.53) between the official laboratory report and the cytopathologist's assessment of inflammation.

There are no uniformly accepted criteria for the presence of inflammation on Papanicolaou smears. In the Bethesda system[13] for reporting cervical and vaginal cytologic findings, evidence of inflammation is encompassed in the descriptive diagnostic category of "benign cellular changes." The subcategory "infection" allows for the diagnosis of specific organisms, such as *Trichomonas*, based on distinctive cytologic characteristics but does not specify criteria for inflammation. Similarly, the subcategory "reactive changes" includes "inflammation" without providing a definition. The scoring system for the cytologic diagnosis of inflammation developed for use in this study is similar to the criteria for inflammation used in the study by Lawley, et al.[12] Both sets of criteria are based on the quantity of leukocytes and the extent to which leukocytes obscure epithelial cells and do not address the presence of "cellular atypia" or other "reactive changes." The results of this study might have been different if the scoring system for inflammation had incorporated these other elements.

In addition to the absence of standardized criteria for evidence of inflammation on Papanicolaou smear, there are other weaknesses of this study. As the study sample was limited to women

who were delivered at one university hospital, additional studies should explore the hypothesis of interest in other populations. The collection of data for analysis was retrospective rather than prospective, but a retrospective study design is unlikely to have resulted in biased measurement of the primary outcome variable. Errors in the assessment of gestational age at delivery are likely to be random, not systematic; there is no reason to believe that misclassification of this outcome was related to the presence or absence of inflammation on Papanicolaou smear. Nevertheless, incomplete or erroneous assessment of important variables is a potential problem when charts are used as the data source. For example, accurate measurement of urinary tract infections and vaginal infections based on chart review is problematic. In this study, criteria for the presence of a urinary tract infection were liberal; a positive urine culture was not required. The variable analyzed in this study was the presence of antibiotic treatment for a presumed urinary tract infection rather than the presence of a documented urinary tract infection. Finally, the possibility of confounding by some unmeasured variable cannot be excluded.

Women who have previously given birth preterm are at increased risk of a subsequent preterm delivery. Little is known about factors that further enhance risk in this already high-risk group. The results of this study suggest that evidence of cervical inflammation on cytologic examination delineates a subgroup that has even higher risk of preterm delivery. The findings further suggest that the association of cervical inflammation with preterm delivery is particularly strong in women considered to have a urinary tract infection during pregnancy. Additional research is needed to confirm these findings and, if confirmed, to clarify the pathophysiology and to evaluate clinical strategies and interventions.

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