

Does Evidence Of Inflammation On Papanicolaou Smears Of Pregnant Women Predict Preterm Labor And Delivery?

Robert L. Blake, Jr., M.D., John W. Gay, M.D., M.P.H., Sharla Brown, and William Smith, M.D.

Abstract: Background: Preterm delivery is the most common cause of neonatal morbidity and mortality in the United States. There is evidence that cervicovaginal infection could predispose to preterm labor. This study explored a possible association of evidence of inflammation on an otherwise normal Papanicolaou smear obtained during pregnancy with subsequent preterm labor and preterm delivery.

Methods: Using a retrospective matched cohort design, we studied women who gave birth to live singleton infants at the University of Missouri Hospital and Clinics during a 21-month period. Papanicolaou smears were obtained from 1 to 8 months before delivery and were interpreted in the same cytopathology laboratory. Data pertaining to outcome variables and potential confounding variables were collected from hospital charts.

Results: Incidence rates were 14.4 percent for labor < 37 weeks' gestation (preterm labor), 12.3 percent for hospitalization for preterm labor, 9.9 percent for delivery < 37 weeks (preterm delivery), 2.6 percent for delivery < 34 weeks, and 7.5 percent for birth weight < 2500 g. On univariate and multivariate analyses, there were no significant differences in any outcome between the 293 women with inflammation and the 284 women without inflammation on Papanicolaou smear. Results were unchanged when the analysis was limited to the 412 women who received no antibiotics during pregnancy. Among the 38 women with a history of preterm labor or preterm delivery, those with cervical inflammation had a higher rate of preterm labor than those without inflammation.

Conclusions: In the sample as a whole, there was little evidence that findings of inflammation on Papanicolaou smear constituted a risk factor for preterm labor or preterm delivery. The data suggest that inflammation could be associated with an increased risk in a subgroup of women at higher risk by virtue of their obstetric history. (J Am Board Fam Pract 1992; 5:555-63.)

Delivery before 37 weeks' gestation is the most common cause of neonatal morbidity and mortality in the United States.¹ Efforts to single out women at high risk for preterm labor using multifactorial scoring systems have yielded mixed and generally disappointing results.²⁻⁶ There is accumulating evidence that cervicovaginal infection plays an important role in initiating preterm labor.⁷⁻⁹ This evidence includes the finding of an increased rate of histologic chorioamnionitis in women with preterm delivery compared with

women with term delivery,¹⁰ the presence of microorganisms in the amniotic fluid of women with preterm labor,¹¹⁻¹⁸ the association of specific cervical or vaginal microorganisms with preterm delivery,^{15,19-23} and a reduction in the rate of prematurity in women treated with antibiotics.²³⁻²⁶ Additional support for the causative role of infection is provided by the finding that a variety of microorganisms produce phospholipase A₂,²⁷ an enzyme that releases arachidonic acid from fetal membranes²⁸ and, thus, initiates synthesis of prostaglandins, which are thought to stimulate parturition.

Evidence of inflammation is a relatively common finding on cervical Papanicolaou smears.²⁹ The clinical importance of the finding of leukocytes on such smears is uncertain, but the finding could indicate the presence of infection. A British

Submitted, revised, 22 June 1992.

From the Department of Family and Community Medicine, and the Department of Obstetrics and Gynecology, University of Missouri-Columbia. Address reprint requests to Robert L. Blake, Jr., M.D., M222 Medical Sciences, Department of Family & Community Medicine, University of Missouri-Columbia, Columbia, MO 65212.

study of 102 women from primary care settings who had inflammatory changes on Papanicolaou smears found *Gardnerella vaginalis* in 43 percent, *Mycoplasma hominis* or *Ureaplasma* in 32 percent, *Candida albicans* in 19 percent, and *Chlamydia trachomatis* in 18 percent.³⁰ Only 25 percent had no evidence of cervical infection. In contrast, a study of asymptomatic women in a United States primary care setting compared 28 women with inflammation on Papanicolaou smear with 262 women without inflammation with respect to the presence of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Candida* species, and *Gardnerella vaginalis*.³¹ The rates of *Chlamydia* and *Trichomonas* infections were higher in women with inflammation, but the predictive value of inflammation for cervical infection was low; 71.4 percent of the women with inflammation had none of the pathogens cultured.

Cytologic examination of the cervix is a routine component of prenatal care. Thus, physicians commonly have available information about the presence or absence of cervical inflammation in pregnant women. In view of the evidence suggesting a causative role for cervicovaginal infection in preterm labor, this information from the Papanicolaou smear could be useful in selecting women who would benefit from more specific diagnostic surveillance for infection. This study explored the hypothesis that pregnant women with evidence of inflammation on otherwise normal cervical Papanicolaou smears have an increased rate of preterm labor and preterm delivery.

Methods

This was a retrospective matched cohort study with data collected from hospital medical records.

Study Sample

Women who gave birth to a live infant at the University of Missouri Hospital and Clinics in Columbia, Missouri, between 1 January 1988 and 30 September 1989 and who had a cervical Papanicolaou smear obtained during pregnancy and interpreted in the hospital cytopathology laboratory were eligible for the study. Patients were excluded if the Papanicolaou smear had been obtained within 30 days of delivery or if the cytopathology laboratory reported any of the following findings on the smear: dysplasia, carcinoma, *Candida*, *Trichomonas*, *Hemophilus*, and *Gardnerella*. As

the research question addressed the predictive value of findings of inflammation on otherwise normal Papanicolaou smears, smears with evidence of a specific reason for the inflammation were excluded. Women who had a repeat Papanicolaou smear obtained after an initial abnormal or suspect Papanicolaou smear were also excluded. Patients eligible for this study were selected through examination of computerized discharge diagnoses and Papanicolaou smear reports. Obstetric care was provided by either obstetricians or family physicians on the attending staff or residency staff of the hospital.

During the 21-month period, 1357 women gave birth to living infants and had received cervical cytological screening during their pregnancies. Of these, 430 (31.7 percent) had findings of inflammation on the Papanicolaou smear. Of the women who had inflammation on the smear, 295 (68.6 percent) met eligibility criteria and constituted the exposed cohort. An unexposed or control cohort was assembled using three criteria of matching: age within 3 years, delivery within 30 days, and the presence or absence of endocervical cells on Papanicolaou smear. For each woman who had inflammation on Papanicolaou smear, a woman who had no inflammation was selected who met these matching criteria.

Independent Variable

The independent variable was presence or absence of inflammation on an otherwise negative Papanicolaou smear. During the 21-month study, cervical specimens for cytologic examination were obtained using a cotton swab and Ayre wooden spatula. During the time of the study, there were no explicit uniform criteria used in the cytopathology laboratory to determine the presence or absence of inflammation on Papanicolaou smears. A report of inflammation was based on the presence of leukocytes only and was not dependent on the presence of cellular atypia or other cytopathologic findings. Generally, inflammation was considered present if at least 25 to 50 percent of the epithelial cells were covered by leukocytes.

Outcome Variables

Outcome events of major interest were onset of labor before 37 weeks' gestational age (preterm labor), hospitalization for preterm labor, delivery

at less than 37 weeks' gestational age (preterm delivery) and birth weight less than 2500 g. Outcome variables of secondary interest included gestational age at delivery, birth weight, and induction of labor before 37 weeks for chorioamnionitis or other complications. Gestational age at onset of labor and at delivery was recorded in the chart by the responsible physician. In a great majority of cases, gestational age was based on a combination of last menstrual period and a sonogram taken before 30 weeks' gestation. In determining gestational age at delivery, numbers that contained fractions of weeks were rounded to the nearest whole week.

Data Collection

Data were collected from patient hospital records by 2 reviewers, a 2nd-year resident in obstetrics and gynecology and a 2nd-year medical student. The medical student received special training to recognize relevant information in the charts. Using uniform definitions and criteria, the reviewers abstracted chart data onto a coding sheet that was specifically developed for this study. Information pertaining to the following was collected for each patient: demographic factors, behavioral and lifestyle characteristics, obstetric history, certain events occurring during pregnancy, and pregnancy outcomes. Information about 47 separate variables was collected from each chart.

Criteria for the presence of preterm labor were liberal. A notation of any action taken in response to preterm labor or possible preterm labor qualified the patient as having had preterm labor. When preterm labor was considered to be present, information about management was extracted from the charts. The reviewer recorded whether the patient was treated with hydration or sedation only, treated with terbutaline, treated with magnesium sulfate, treated with nifedipine, treated with another tocolytic agent, and admitted to the hospital.

To assess interviewer reliability, 30 patient charts (5 percent of the total) were reviewed independently by the 2 reviewers. The rate of agreement across all 47 variables was 96.2 percent. There was 100 percent agreement for the following outcomes: gestational age at delivery, preterm delivery, birth weight, and induction of labor before 37 weeks. There was agreement on the pres-

ence or absence of preterm labor in 93.3 percent of these charts. The Cohen kappa statistic for preterm labor was 0.81, indicating a high level of reliability.

Data Analysis

Data were processed and analyzed using SPSS-PC version 4.0.³² 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 measure of association, the relative risk, was calculated by dividing the rate of an outcome in the exposed group by the rate in the control group. The test-based method³³ was used to calculate 95 percent confidence limits to the point estimate of relative risk.

To control for possible confounding by other variables, multivariate analyses were conducted using logistic regression models. A regression model was constructed for each of the following dependent variables: preterm labor, hospitalization for preterm labor, preterm delivery, and birth weight less than 2500 g. The dichotomous exposure variable (inflammation versus no inflammation on Papanicolaou smear) was included as an independent variable in each model. In addition, variables that were associated, on univariate analyses, with a particular outcome variable with $P \leq 0.15$ were included as independent variables in the model used to predict that dependent variable. The liberal criteria of $P \leq 0.15$ was selected to assure adjustment for all potential confounding variables. Adjusted odds ratios were calculated by using regression coefficients (betas). In the univariate and multivariate analyses of the possible association of the exposure variable of interest (inflammation versus no inflammation on Papanicolaou smear) with each outcome variable, $P \leq 0.05$ was considered the criterion for statistical significance.

In the absence of statistically significant associations, power calculations³⁴ explored the ability of the study to detect a doubling of the crude rates of adverse outcomes in patients with inflammation compared with those without inflammation.

Results

Patient Characteristics

Hospital charts of 4 patients in the control group could not be located or were not available. Nine

patients had a multiple gestation; 2 were in the exposed group and 7 were in the control group. Because of the strong association of multiple gestation with preterm labor and preterm delivery,³⁵ these cases were excluded from the analysis.

Table 1 shows a comparison of the 293 patients with inflammation and the 284 patients without inflammation with respect to a variety of characteristics. Compared with the control group, patients with evidence of inflammation on Papanicolaou smear had higher rates of gravidity and parity, were less likely to be primiparous, were more frequently treated with systemic antibiotics before labor, and were more likely to have a urinary tract infection during pregnancy. Because Papanicolaou smears were usually obtained on the first prenatal visit, the difference in gestational age at Papanicolaou smear suggests that women with inflammation presented for care somewhat later in pregnancy than those without inflammation. None of the women had abdominal surgery during pregnancy, and only 1 had a history of diethylstilbestrol (DES) exposure. Prevalences of the following characteristics were less than 3 percent and were similar in the two groups: more than one first-trimester-induced abortion, a second-trimester-induced abortion, a stillbirth, illegal drug use, history of cone biopsy, hydramnios, acute pyelonephritis during pregnancy, and febrile illness during pregnancy.

In a modification of the risk scoring system of Holbrook, et al.,⁶ we constructed a risk variable that aggregated information pertaining to nine characteristics. Women were considered to be at high risk of preterm labor if they had one or more of the following: previous preterm delivery, previous preterm labor with term delivery, past DES exposure, cigarette smoking greater than 1/2 pack per day, previous cone biopsy, uterine anomaly, hydramnios, and febrile illness. As indicated in Table 1, high-risk women were equally distributed between the two groups.

Outcomes

For the 577 women with singleton deliveries, the incidence of preterm labor was 14.4 percent, the incidence of hospitalization for preterm labor, 12.3 percent; preterm delivery, 9.9 percent; birth weight less than 2500 g, 7.5 percent; and induction of labor before 37 weeks for chorioamnionitis or other complications, 1.2 percent. Of the

Table 1. Sociodemographic and Medical Characteristics.

Characteristic	Inflam- mation (n = 293)	No Inflam- mation (n = 284)	P Value*
	Means		
Gestational age at Papanicolaou smear (wk)	16.3	14.7	0.006
Maternal age at delivery (yr)	24.5	24.4	0.75
Gravidity	2.6	2.3	0.01
Parity	1.1	0.9	0.02
Education (yr)	12.3	12.4	0.46
Percentages			
White	81	82	0.64
Married	65	71	0.11
Medical insurance	41	41	0.95
Primiparous	26	36	0.007
Previous preterm delivery	4	5	0.93
Previous preterm labor with term delivery	2	2	0.95
Cigarette smoking: none	65	67	
< 1/2 pack per day	5	5	0.88
≥ 1/2 pack per day	30	28	
Regular use of alcohol	12	12	0.79
Cervical gonococcal culture positive†	0.4	1	0.35
Cervical <i>Chlamydia</i> test positive†	5	5	0.91
Antibiotic treatment during pregnancy‡	35	22	0.001
Urinary tract infection during pregnancy	17	11	0.03
High risk§	36	34	0.55

*Analysis of variance for comparison of means; chi-square or Fisher exact test for comparison of proportions.

†Denominators are numbers of women who had test performed. For gonococcal culture, n = 238 (inflammation) and n = 216 (no inflammation). For *Chlamydia* test, n = 119 (inflammation) and n = 90 (no inflammation).

‡Treatment with systemic antibiotics, including metronidazole, during pregnancy but before onset of labor. Does not include intravaginal creams or suppositories.

§Patients were considered high risk if they had one or more of the following: previous preterm delivery, previous preterm labor with term delivery, past diethylstilbestrol exposure, smoking ≥ 1/2 pack per day, previous cone biopsy, uterine anomaly, hydramnios, and febrile illness.

83 patients with a diagnosis of preterm labor, 85.5 percent were hospitalized (as opposed to being observed for several hours and sent home), 68.7 percent received terbutaline, 15.7 percent received magnesium sulfate, 4.8 percent received nifedipine, 3.6 percent received another tocolytic

agent, and 2.4 percent were given hydration or sedation alone. Of the women hospitalized for preterm labor, 29.6 percent received no therapy designed to stop labor. One-half (48 percent) of the women considered to have preterm labor gave birth before 37 weeks.

On univariate analysis, evidence of inflammation on Papanicolaou smear was not associated with any outcome variable (Table 2). The relative risk in exposed compared with control women was 1.26 (95 percent confidence interval [CI] 0.85 to 1.88) for preterm labor, 1.26 (95 percent CI 0.81 to 1.95) for hospitalization for preterm labor, 1.55 (95 percent CI 0.94 to 2.57) for preterm delivery, and 0.94 (95 percent CI 0.55 to 1.59) for low birth weight. Mean gestational age at delivery and mean birth weight were similar in the two groups. There was a tendency for women in the control group to have a higher rate of induction before 37 weeks ($P = 0.07$) for chorioamnionitis or other complications. Women in the two groups were equally likely to receive tocolytic medications after hospitalization ($P = 0.93$) and were equally likely to be delivered preterm after hospitalization ($P = 0.73$). There was no significant difference between the groups in the incidence of delivery before 34 weeks' gestation (2.7 percent versus 2.5 percent, $P = 0.87$). There were no differences between the exposed and control groups on any outcome when the analysis was limited to the 412 women who received no antibiotics during pregnancy.

Table 3 presents the variables that were associated with one or more of the outcome variables

Table 3. Predictors of Pregnancy Outcomes on Univariate Analysis.

Characteristic	Hospitalization for		Birth	
	Preterm Labor (n = 83)	Preterm Labor (n = 71)	Preterm Delivery (n = 57)	Weight < 2500 g (n = 43)
Education ≤ 12 yr	0.005*	0.01	NS*	0.09
Gravidity > 1	0.10	NS	0.10	NS
Parity ≥ 1	0.15	NS	0.11	NS
Stillbirth	NS	NS	NS	0.02
Previous preterm labor or delivery†	0.00001	0.0002	0.003	NS
Smoking $\geq 1/2$ pack per day	0.15	NS	NS	0.03
Alcohol use	NS	NS	NS	0.004
Illegal drugs	NS	NS	NS	0.00005
Antibiotic treatment	0.06	0.03	NS	NS
Urinary tract infection	0.03	0.03	0.11	NS
Acute pyelonephritis	NS 0.03	NS	0.15	0.001
High risk‡	0.04	0.09	NS	0.002

*Numbers in the table are P values based on chi-square with 1 degree of freedom or on Fisher exact tests. NS = nonsignificant ($P > 0.15$)

†This composite variable was considered positive if the patient had either a previous preterm delivery or previous preterm labor with term delivery.

‡Patients were considered high risk if they had one or more of the following: previous preterm delivery, previous preterm labor, with term delivery, past diethylstilbestrol exposure, smoking $\geq 1/2$ pack per day, previous cone biopsy, uterine anomaly, hydramnios, and febrile illness.

Table 2. Outcomes of Pregnancy in Patients with and without Inflammation on Papanicolaou Smear.

Outcome	Inflam- mation (n = 293)	No Inflam- mation (n = 284)	P Value*
	Incidence (per 100)		
Preterm labor	16.0	12.7	0.25
Hospitalization for preterm labor	13.7	10.9	0.32
Preterm delivery	11.9	7.7	0.09
Birth weight < 2500 g	7.2	7.7	0.79
	Means		
Gestational age (wk)	39.0	38.9	0.55
Birth weight (g)	3336.0	3277.0	0.24

*Chi-square for comparison of incidences; analysis of variance for comparison of means.

with $P \leq 0.15$. For these univariate analyses, the education variable was dichotomized (> 12 years versus ≤ 12 years) and the variables "previous preterm delivery" and "previous preterm labor with term delivery" were combined into a single variable.

Logistic regression analyses were performed with each of the four pregnancy outcomes considered as a dependent variable. In each model variables that were associated with the dependent variable on univariate analysis with $P \leq 0.15$ were included as independent variables. Because of the high correlation of gravidity with parity, only gravidity was entered into the models. On multivariate analysis, inflammation on Papanico-

laou smear was not associated with any of the pregnancy outcomes. Adjusted odds ratios for this independent variable were 1.11 (95 percent CI 0.66 to 1.83) for preterm labor, 1.20 (95 percent CI 0.70 to 2.07) for hospitalization for preterm labor, 1.53 (95 percent CI 0.86 to 2.71) for preterm delivery, and 0.70 (95 percent CI 0.32 to 1.29) for low birth weight. These values are similar to the crude relative risks, indicating little confounding by other variables.

Table 4 shows the independent variables that were statistically significantly associated with pregnancy outcomes on multivariate analysis. Previous preterm labor or preterm delivery and low education were each independently associated with preterm labor and hospitalization for preterm labor. Previous preterm labor or delivery was the only statistically significant risk factor for preterm delivery. Previous stillbirth and acute pyelonephritis during pregnancy were associated with low birth weight.

A series of stratified analyses explored the possible association of cervical inflammation with pregnancy outcomes in subgroups defined by the presence or absence of recognized risk factors for preterm labor. There were no statistically significant associations of inflammation with any outcome variable among either primiparous or multiparous women, women with low (≤ 12 years) or high (> 12 years) education levels, women without a history of preterm labor or preterm delivery, and women with low Holbrook, et al.⁶ risk scores. Among the 38 women with a history of preterm labor or preterm delivery, the rates of preterm labor (57.9 percent versus 21.1 percent, $P = 0.02$)

and hospitalization for preterm labor (47.4 percent versus 15.8 percent, $P = 0.03$) were higher in women with inflammation than without inflammation. Similarly, among women who were at high risk on the basis of the Holbrook, et al. scoring system, those with evidence of inflammation on Papanicolaou smear had higher rates of preterm labor (24.8 percent versus 11.6 percent, $P = 0.02$), hospitalization for preterm labor (21.0 percent versus 9.5 percent, $P = 0.03$), and preterm delivery (15.2 percent versus 6.3 percent, $P = 0.05$).

The alternative hypothesis that the presence of inflammation on the Papanicolaou smear doubled the incidence of each pregnancy outcome was explored with power analyses. The power of the study to detect doubling of the crude incidence rate was 0.89 for preterm delivery and greater than 0.95 for preterm labor, hospitalization for preterm labor, and low birth weight. Thus, it is unlikely that the relative risk for any of these outcomes is as high as 2.0.

Discussion

In the overall sample, women who had evidence of inflammation on an otherwise negative Papanicolaou smear during pregnancy did not have a significantly higher rate of preterm labor, preterm delivery, or low birth weight. On an average, Papanicolaou smears were obtained more than 5 months before delivery, and all were obtained at least 30 days before delivery. The 30-day limit was set as an eligibility criterion to allow sufficient time for clinical interventions if an association between inflammation and an adverse pregnancy outcome was found. This study did not address the potential predictive value of Papanicolaou smears obtained late in pregnancy. In practice, cervical cytologic screening is usually performed during the first half of pregnancy.

The results of the exploratory subgroup analyses must be interpreted cautiously because of the increased risk of type I errors that result from multiple comparisons. Among women with a history of preterm labor or preterm delivery or at high risk by the scoring system of Holbrook, et al.,⁶ those with inflammation had higher rates of certain adverse outcomes than those without inflammation. These findings suggest that cervical inflammation could confer incremental risk for pregnant women who have other risk factors for

Table 4. Predictors of Pregnancy Outcomes on Multivariate Analysis (Odds Ratio*).

Predictor	Preterm Labor	Hospitalization for Preterm Delivery	Preterm Delivery	Birth Weight ≤ 2500 g
Previous preterm labor or delivery	5.23	5.29	2.75	—
Previous stillbirth	—	—	—	8.00
Acute pyelonephritis	—	—	—	7.90
Education ≤ 12 yr	2.24	2.00	—	—

*All odds ratios are statistically significantly different from 1.0 with $P < 0.05$.

preterm labor and preterm delivery. As these findings resulted from post hoc analyses of subgroups, they are very tentative and should be used only to formulate hypotheses for future investigation.

The retrospective nature of this study imposed several important methodologic limitations. There were no uniform explicit criteria for the presence of inflammation on Papanicolaou smears or for the diagnosis of preterm labor. It is quite likely that some women were erroneously labeled as having preterm labor. The group of women who were hospitalized for management of preterm labor is probably a more accurate approximation of women who actually experienced this event. The rate of hospitalization for preterm labor in our sample is similar to rates of preterm labor found in prospective studies that used standardized criteria for diagnosis.^{6,21} In addition, the proportion of women with preterm labor who gave birth before term (48 percent) in our study is comparable with that found in other studies.^{36,37} Also, there is no reason to suspect that women with cervical inflammation earlier in pregnancy would be more or less likely to be misclassified with respect to preterm labor. Thus, any misdiagnosis of preterm labor would be expected to be random rather than systematic in relation to the presence of inflammation.

In this retrospective study, we did not attempt to determine the status of the fetal membranes at the onset of preterm labor. Thus, we were not able to assess the rate of preterm rupture of membranes in the exposed and control groups. It is likely that many of the women with preterm labor who did not receive tocolytic therapy had ruptured membranes. Women who did not receive tocolysis were similarly distributed among the exposed and control groups. This finding suggests that the rates of preterm rupture of membranes with preterm labor were similar in the groups.

Physicians who provided prenatal care to the study subjects were aware of Papanicolaou smear results. The presence of inflammation on Papanicolaou smear was occasionally noted in the prenatal record. Evidence that this finding evoked any diagnostic or therapeutic response was very rare. In most cases, the finding of inflammation on Papanicolaou smear seemed to be ignored by the physician managing the patient.

Women with inflammation on smears were more likely to be tested for gonorrhea and for

Chlamydia. Screening for these organisms, using Thayer-Martin agar and the Chlamydiazyme test, was performed at the discretion of the physician. Screening for these organisms usually, but not always, occurred at the time the Papanicolaou smear was obtained. It is possible that physicians were motivated more frequently to screen for gonorrhea and *Chlamydia* in women who had inflammation on Papanicolaou smear because of the gross appearance of the cervix at the time of pelvic examination. Interestingly, the rate of infection with gonorrhea and with *Chlamydia* was similar in women with and without inflammation on Papanicolaou smears. The rate of gonorrhea in this sample was similar to that found in other studies^{19,21}; the rate of *Chlamydia* was similar to that found in some studies²³ but lower than rates found in others.^{21,38}

Women with inflammation on Papanicolaou smear were more likely to be treated with systemic antibiotics during pregnancy. This difference is only partially explained by the higher rate of urinary tract infections in women with inflammation on Papanicolaou smear. The most commonly prescribed antibiotics were ampicillin or amoxicillin (54 percent of women receiving an antibiotic), metronidazole (24 percent), erythromycin (19 percent) and nitrofurantoin (11 percent). It is possible that the use of antibiotics changed the natural history of cervical inflammation and mitigated its effect on pregnancy outcome. When the analysis was restricted to women who were not treated with systemic antibiotics during pregnancy, however, there was still no association of the presence of inflammation on Papanicolaou smear with preterm labor or preterm delivery. The use of topical vaginal preparations was not assessed; their effect on microorganisms implicated in the onset of preterm labor is dubious.³⁹

Women whose Papanicolaou smears showed a specific microorganism (i.e., *Trichomonas*) were excluded from the study for several reasons. The sensitivity and specificity of such findings are uncertain. Because only a few women had any particular microorganism, the statistical power to detect differences in any outcome would be low. Also, many women received treatment based on the Papanicolaou smear report, thus obscuring the natural history of the infection in terms of effect on pregnancy outcome.

In the sample as a whole, the presence of inflammation on Papanicolaou smear during pregnancy was not associated with a significantly increased incidence of preterm labor or preterm delivery. There was a reasonable statistical power to detect a relative risk of 2.0 for each major outcome. The findings raise the possibility that cervical inflammation could contribute additional risk for a subgroup of women who are at higher risk because of other characteristics. This possibility could be explored in a prospective study that used explicit criteria for the presence of inflammation and for preterm labor.

References

- McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *N Engl J Med* 1985; 312:82-90.
- Creasy RK, Gummer BA, Liggins GC. System for predicting spontaneous preterm birth. *Obstet Gynecol* 1980; 55:692-5.
- Fortney JA, Whitehorn EW. The development of an index of high-risk pregnancy. *Am J Obstet Gynecol* 1982; 143:501-8.
- Main DM, Gabbe SG, Richardson D, Strong S. Can preterm deliveries be prevented? *Am J Obstet Gynecol* 1985; 151:892-8.
- Main DM, Richardson D, Gabbe SG, Strong S, Weller SC. Prospective evaluation of a risk scoring system for predicting preterm delivery in black inner city women. *Obstet Gynecol* 1987; 69:61-6.
- Holbrook RH Jr, Laros RK Jr, Creasy RK. Evaluation of a risk-scoring system for prediction of preterm labor. *Am J Perinatol* 1989; 6:62-8.
- Romero R, Mazor M. Infection and preterm labor. *Clinical Obstet Gynecol* 1988; 31:553-84.
- Romero R, Mazor M, Wu YK, Sirtori M, Oyarzun E, Mitchell MD, et al. Infection in the pathogenesis of preterm labor. *Semin Perinatol* 1988; 12:262-79.
- Ledger WJ. Infection and premature labor. *Am J Perinatol* 1989; 6:234-6.
- Guzick DS, Winn K. The association of chorioamnionitis with preterm delivery. *Obstet Gynecol* 1985; 65:11-6.
- Miller JM, Pupkin MJ, Hill GB. Bacterial colonization of amniotic fluid from intact fetal membranes. *Am J Obstet Gynecol* 1980; 136:796-804.
- Bobitt JR, Hayslip CC, Damato JD. Amniotic fluid infection as determined by transabdominal amniocentesis in patients with intact membranes in premature labor. *Am J Obstet Gynecol* 1981; 140:947-52.
- Wahbeh CJ, Hill GB, Eden RD, Gall SA. Intra-amniotic bacterial colonization in premature labor. *Am J Obstet Gynecol* 1984; 148:739-43.
- Hameed C, Tejani N, Verma UL, Archbald F. Silent chorioamnionitis as a cause of preterm labor refractory to tocolytic therapy. *Am J Obstet Gynecol* 1984; 149:726-30.
- Gravett MG, Hummel D, Eschenbach DA, Holmes KK. Preterm labor associated with subclinical amniotic fluid infection and with bacterial vaginosis. *Obstet Gynecol* 1986; 67:229-37.
- Iams JD, Clapp DH, Contos DA, Whitehurst R, Ayers LW, O'Shaughnessy RW. Does extra-amniotic infection cause preterm labor? Gas liquid chromatography studies of amniotic fluid in amnionitis, preterm labor, and normal controls. *Obstet Gynecol* 1987; 70:365-8.
- Romero R, Quintero R, Oyarzun E, Wu YK, Sabo V, Mazor M, et al. Intraamniotic infection and the onset of labor in preterm premature rupture of the membranes. *Am J Obstet Gynecol* 1988; 159:661-6.
- Skoll MA, Moretti ML, Sibai BM. The incidence of positive amniotic fluid cultures in patients in preterm labor with intact membranes. *Am J Obstet Gynecol* 1989; 161:813-6.
- Edwards LE, Barrada MI, Hamann AA, Hakanson EY. Gonorrhea in pregnancy. *Am J Obstet Gynecol* 1978; 132:637-41.
- Regan JA, Chao S, James LS. Premature rupture of membranes, preterm delivery, and group B streptococcal colonization of mothers. *Am J Obstet Gynecol* 1981; 141:184-6.
- Gravett MG, Nelson HP, DeRouen T, Critchlow C, Eschenbach DA, Homes KK. Independent associations of bacterial vaginosis and *Chlamydia trachomatis* infection with adverse pregnancy outcome. *JAMA* 1986; 256:1899-903.
- Martius J, Krohn MA, Hillier SL, Stam WE, Homes KK, Eschenbach DA. Relationships of vaginal *Lactobacillus* species, cervical *Chlamydia trachomatis*, and bacterial vaginosis to preterm birth. *Obstet Gynecol* 1988; 71:89-95.
- Cohen I, Veille JC, Calkins BM. Improved pregnancy outcome following successful treatment of chlamydial infection. *JAMA* 1990; 263:3160-3.
- Kass EH, McCormick WM, Lin JS, Rosner B, Munoz A. Genital mycoplasmas as a cause of excess premature delivery. *Trans Assoc Am Physicians* 1981; 94:261-6.
- McGregor JA, French JI, Reller LB, Todd JK, Makowski EL. Adjunctive erythromycin treatment for idiopathic preterm labor: results of a randomized, double-blinded, placebo-controlled trial. *Am J Obstet Gynecol* 1986; 154:98-103.
- Morales WJ, Angel JL, O'Brien WF, Knuppel RA, Finazzo M. A randomized study of antibiotic therapy in idiopathic preterm labor. *Obstet Gynecol* 1988; 72:829-33.
- Bejar R, Curbelo V, Davis C, Gluck L. Premature labor. II. Bacterial sources of phospholipase. *Obstet Gynecol* 1981; 57:479-82.
- Takahashi K, Imai A, Tamaya T. Preterm labor and bacterial intra-amniotic infection: arachidonic acid

- liberation by the action of phospholipase A₂. Arch Gynecol Obstet 1988; 244:1-6.
29. Lawley TB, Lee RB, Kapela R. The significance of moderate and severe inflammation on class I Papanicolaou smear. Obstet Gynecol 1990; 76: 997-9.
 30. Wilson JD, Robinson AJ, Kinghorn SA, Hicks DA. Implications of inflammatory changes on cervical cytology. BMJ 1990; 300:638-40.
 31. Bertolino JG, Rangel JE, Blake RL, Silverman D, Ingran E. Inflammation on the cervical Papanicolaou smear: the predictive value for infection in the asymptomatic woman. Fam Med 1992; 24:447-52.
 32. Norusis MJ. SPSS/PC+ advanced statistics 4.0. Chicago: SPSS, 1990.
 33. Rothman KJ. Modern epidemiology. Boston: Little, Brown, 1986:145-7.
 34. Feinstein AR. Clinical biostatistics. St. Louis: C.V. Mosby, 1977:326-30.
 35. Keith L, Ellis R, Berger GS, Depp R. The Northwestern University multihospital twin study, I. A description of 588 twin pregnancies and associated pregnancy loss, 1971 to 1975. Am J Obstet Gynecol 1980; 138:781-9.
 36. Creasy RK. Prevention of preterm birth. Birth Defects 1983; 19:97-102.
 37. Newton ER, Dinsmoor MJ, Gibbs RS. A randomized, blinded, placebo-controlled trial of antibiotics in idiopathic preterm labor. Obstet Gynecol 1989; 74:562-6.
 38. Maguire NC, Jordan AG, Ehya H. Detection of *Chlamydia trachomatis* in cervical smears from pregnant population. Arch Pathol Lab Med 1990; 114:204-7.
 39. Grossman JH III, Larsen JW Jr. Pelvic infections. In: Kase NG, Weingold AB, Gershenson DM, editors. Principles and practice of clinical gynecology. 2nd edition. New York: Churchill Livingstone, 1990:583-96.