Low Birth Weight, Prematurity, and Postpartum Endometritis

Association With Prenatal Cervical *Mycoplasma hominis* and *Chlamydia trachomatis* Infections

Stuart M. Berman, MD; H. Robert Harrison, DPhil, MD, MPH; W. Thomas Boyce, MD; William J. J. Haffner, MD; Marguerite Lewis, RN; Julia Barney Arthur, RN

We studied associations of *Mycoplasma hominis, Ureaplasma urealyticum,* and *Chlamydia trachomatis* genital infections with pregnancy outcomes, controlling by logistic and multiple linear regression for known risk factors and for the presence of the other two infections. A sample of 1204 Navajo women enrolling for prenatal care had endocervical *C trachomatis, M hominis,* and *U urealyticum* cultures and serum samples taken at enrollment and when possible after 30 weeks. Low birth weight (<2500 g) was associated with *M hominis* infection among women with a history of spontaneous abortion. *Mycoplasma hominis* infection was also associated with postpartum endometritis, but only among women undergoing a cesarean section (odds ratio, 4.7; 95% confidence intervals, 1.22 to 18.3). Although women with recent *C trachomatis* infection (IgM titer>1:32 on either sample or IgG seroconversion) were at greater risk of low birth weight (19% [3/16]) than women with chronic infection (4.5% [6/133]; relative risk, 4.2), this subgroup at risk was small (11% of women with classifiable *C trachomatis* infection). *Mycoplasma hominis* and *C trachomatis* infections may be important preventable causes of adverse pregnancy outcomes in identifiable subgroups of women.

(*JAMA* 1987;257:1189-1194)

BECAUSE low birth weight is a major predictor of neonatal mortality and morbidity,[1] identifying preventable causes and thereby decreasing the incidence of low birth weight are major public health goals. Since Elder et al[2] first demonstrated that the risk of low birth weight (<2500 g) among women without bacteriuria was reduced by tetracycline, numerous investigators have sought to clarify the relationship between genitourinary tract infections and adverse pregnancy outcomes. Several studies have found low birth weight and other adverse outcomes associated with genital infections of *Mycoplasma hominis, Ureaplasma urealyticum,*[3] or *Chlamydia trachomatis.*[4] Unfortunately, the results of these studies have been inconsistent. Although some studies have demonstrated associations of these organisms with spontaneous abortion, low birth weight, decreased mean birth weight, preterm delivery, neonatal morbidity, or maternal postpartum morbidity,[5-9] other studies have failed to confirm these observations.[10-12]

Explanations for these inconsistencies address issues such as study size, appropriateness of control groups, heterogeneity of populations studied, serological classification of infection, low prevalence in some study populations of the organisms of interest, adequacy of control for a multiplicity of confounding factors, and need to ascertain and control for the presence of coexisting infections.[13,14] We performed a prospective, population-based study in a homogeneous sample of pregnant women who had a high prevalence of *M hominis, C trachomatis,* and *U urealyticum* genital infections. Possible sources of bias present in many previous studies appear to have been avoided in this population and with this study design.

METHODS

The study sample (N = 1204), consisting almost entirely of Navajo women, was obtained at two Indian Health Service sites, located in Gallup and Crownpoint, NM. Women were enrolled in the investigation by a study nurse (J.B.A.) at their initial prenatal care visit; the study population comprised about 60% of all women seeking initial prenatal care at the clinics from Oct 15, 1980, to Oct 15, 1983. Women who sought prenatal care early in pregnancy (<24 weeks' gestation) were overrepresented; the 40% of the women not enrolled either presented later in pregnancy or were excluded because of personnel constraints, not maternal characteristics.

Endocervical cultures for *C trachomatis, M hominis,* and *U urealyticum* were obtained by clinic physicians at the initial prenatal visit and again, if possible, at a prenatal visit during the third trimester. At these visits we also obtained serum samples that were tested for IgG and IgM antibodies to *C trachomatis.* Patient charts and medical records were reviewed two months postpartum by

From the Division of Sexually Transmitted Diseases, Centers for Disease Control, Atlanta (Drs Berman and Harrison); the Department of Pediatrics, College of Medicine, University of Arizona, Tucson (Dr Boyce and Mss Lewis and Arthur); and the Department of Obstetrics and Gynecology, Uniformed Services of the Health Sciences, Gallup, NM (Dr Haffner).

Reprint requests to the Technical Information Services, Center for Prevention Services, Centers for Disease Control, Atlanta, GA 30333.

Table 1.—Comparisons of Characteristics of Women by Site of Enrollment and by Outcome Status: Unavailable for Follow-up vs Single Infant Delivery

	Enrollment (N=1204)					Outcome			
	Gallup, NM (n=949)		Crownpoint, NM (n=254)			Unavailable for Follow-up (n=104)		Live Born Single Infant (n=1041)†	
Characteristic	%	(No.)	%	(No.)	Total, %*	%	(No.)	%	(No.)
Age, y									
Unknown	...	(6)	...	(1)	...	...	(1)	...	(6)
<20	23	(217)	25	(63)	23	27	(28)	24	(243)
20-29	58	(542)	57	(144)	57	59	(61)	57	(591)
>29	20	(184)	18	(46)	19	14	(14)	19	(201)
Total	**101**	**(949)**	**100**	**(254) NS**	**99**	**100**	**(104)**	**100**	**(1041) NS**
Parity									
Unknown	...	(0)	...	(1)	...	...	(1)	...	(0)
0	35	(328)	33	(84)	34	34	(35)	34	(358)
≥1	65	(621)	67	(169)	66	66	(68)	66	(683)
Total	**100**	**(949)**	**100**	**(254) NS**	**100**	**100**	**(104)**	**100**	**(1041) NS**
Enrollment gestation, wk									
Unknown	...	(7)	...	(8)	...	...	(3)	...	(9)
≤12	43	(406)	53	(130)	45	54	(55)	43	(447)
13-23	46	(435)	34	(83)	44	35	(35)	45	(465)
>23	11	(101)	13	(33)	11	11	(11)	12	(120)
Total	**100**	**(949)**	**100**	**(254) $P<.01$**	**100**	**100**	**(104)**	**100**	**(1041) NS**
Education, y									
Unknown	...	(100)	...	(80)	...	...	(16)	...	(150)
<12	48	(410)	56	(97)	50	40	(35)	51	(453)
≥12	52	(439)	44	(77)	50	60	(53)	49	(438)
Total	**100**	**(949)**	**100**	**(254) NS**	**100**	**100**	**(104)**	**100**	**(1041) NS**

*Site unknown (n=1).
†Twins, stillbirths, and abortions (n=59).

Table 2.—Prevalence of Infections by Risk Factor Status Among Enrollees*

		Mycoplasma hominis		*Chlamydia trachomatis*		*Ureaplasma urealyticum*	
Risk Factor	No.	Prevalence, %†	RR‡	Prevalence, %†	RR‡	Prevalence, %†	RR‡
Age ≤29 y	936	51.9	1.2§	23.7	1.7§	83.2	1.2§
Education <12 y	494	53.4	1.1	24.2	1.3§	82.2	1.1
Nulliparous	400	53.8	1.1	24.4	1.2	85.0	1.1§
Unmarried	467	55.7	1.2	22.3	1.0	85.7	1.1§
Prior gonorrhea	133	57.9	1.2§	32.1	1.6§	78.2	1.0
M hominis	586	...	...	31.2	2.4§	90.6	1.3§
C trachomatis	249	71.1	1.6§	...	...	91.2	1.2§
U urealyticum	944	56.7	2.4§	24.6	2.3§	...	...

*N=1204.
†Prevalence of infection among those with risk factor.
‡RR indicates relative risk, ratio of prevalence of organism among those with risk factor to prevalence among those without the factor.
§$P<.05$.

some of the coauthors (H.R.H., W.T.B., M.L., and J.B.A.) who were unaware of the culture results. The charts provided the following information: maternal demographic characteristics, reproductive history, events during pregnancy, length of gestation, pregnancy outcome, duration of labor, duration of ruptured membranes, occurrence of premature rupture of membranes (the occurrence of membrane rupture more than one hour before the onset of labor), number of vaginal examinations while in labor, type of delivery, and postpartum complications (postpartum endometritis and postpartum fever). Postpartum fever was defined as a temperature of 38°C or higher on two occasions occurring more than 24 hours after delivery, without an identifiable source, and postpartum endometritis was defined as postpartum fever accompanied by either cervical discharge or uterine tenderness.

Chlamydia and *Mycoplasma* Cultures

Endocervical specimens were collected with calcium-alginate–tipped swabs, which were immersed in sucrose-phosphate transport medium for culture of *C trachomatis*[15] and in trypticase-soy broth with added bovine serum albumin for culture of *M hominis* and *U urealyticum*.[16] All specimens from both Gallup and Crownpoint were immediately frozen at −70°C and shipped to Tucson on dry ice, where they were stored at −70°C until inoculation. *Chlamydia trachomatis* was cultured in cycloheximide-treated McCoy cells, using a microtiter plate system.[17] Thawed specimens were inoculated into urea broth and onto *E* agar and *Mes* agar plates.[16] *Mycoplasma hominis* was identified by typical morphological features on subculture plates, and *U urealyticum*, by broth passage and calcium chloride stain of subcultured colonies on *Mes* agar.[16]

Chlamydia Serological Studies

Immunoglobulin G and IgM antibodies to *C trachomatis* were measured with the microimmunofluorescence method.[18] Antibody titers for IgG of 1:16 or greater, or for IgM of 1:32 or greater, as measured with fluorescein-conjugated immunoglobulin-class-specific goat anti–human globulins, were regarded as positive. We used serological data to classify *Chlamydia* infections as recent (either specimen IgM positive or IgG seroconversion), chronic (third-trimester specimen both IgG and IgM negative or initial specimen IgG positive and IgM negative), or unknown (unclassifiable because of missing serological data).

Statistical Analysis

Mantel-Haenszel χ^2 test was used to assess differences in proportions and to generate 95% test-based confidence intervals.[19] Differences in mean birth weight were assessed by Student's *t* test.

Logistic regression was used to determine odds ratios for the association of the different infections, *M hominis*, *C trachomatis*, or *U urealyticum*, with pregnancy outcomes. The initial model we employed contained the risk factors of interest, potential confounders, and interaction terms. We determined if the model with all interaction terms differed significantly from the model without interaction terms; only if these models differed significantly were the

Table 3.—Risk of Low Birth Weight (<2500 g) by Infection at Enrollment Among Women Enrolled at Less Than 24 Weeks' Gestation

Infection Status*	Incidence of Low Birth Weight, %†	RR (95% CI)‡
Mycoplasma hominis		
Positive	8.1 (28/344)	1.8 (1.0-3.1)
Negative	4.6 (21/460)	. . .
Chlamydia trachomatis		
Positive	8.6 (12/140)	1.5 (0.8-2.8)
Negative	5.8 (37/641)	. . .
Ureaplasma urealyticum		
Positive	6.5 (36/552)	1.3 (0.7-2.3)
Negative	5.2 (13/249)	. . .

*The number of women whose *M hominis* status was unknown was 88; for *C trachomatis*, 111 women; and for *U urealyticum*, 91 women.
†Overall incidence of low birth weight was 6.2% (55/892).
‡RR indicates relative risk; CI, confidence intervals.

Table 4.—Adjusted Odds Ratio for Low Birth Weight Associated With Infection at Initial Visit*

Risk Factor	Odds Ratio† (95% CI)‡
Chlamydia trachomatis	1.1 (0.5-2.4)
Mycoplasma hominis	
History of abortion	9.4 (1.1-84)
No history of abortion	1.4 (0.6-3.0)
Ureaplasma urealyticum	1.4 (0.6-3.2)

*Enrollment gestation less than 24 weeks (n = 637).
†Controlling, by logistic regression, for parity, age, enrollment gestation, marital status, bleeding during pregnancy, prior abortion, and coexisting *C trachomatis*, *M hominis*, or *U urealyticum* infections.
‡CI indicates confidence intervals.

individual interaction terms evaluated. We retained first-order variables regardless of significance when an interaction term involving that variable was found to be significant.[20,21] By eliminating interaction terms in this fashion, we decreased the likelihood of finding a significant interaction term by chance alone—a possibility associated with multiple testing as performed by backward stepwise elimination.

Multiple linear regression was used to assess the association of the infections with differences in mean birth weight. Associations between cervical infections and pregnancy outcomes (low and mean birth weight, postpartum endometritis, and postpartum fever) were assessed among the women who had single infant births (n = 1041).

Associations With Low Birth Weight

Associations between cervical infections and low birth weight were assessed among women enrolling before 24 weeks' gestation. To avoid bias, we used culture results from the initial visit (available on 781, 801, and 804 enrollees for *C trachomatis*, *U urealyticum*, and *M hominis*, respectively) to define infection. A bias would have been introduced if we defined infection as a positive test result on either first or second culture. Because their pregnancies often terminated before a second culture could be obtained, women who were delivered of low–birth-weight infants were less likely to have been cultured twice than women who were delivered of larger babies. Since the sensitivity of a single endocervical swab is less than 100% (probably 70% to 80%),[22] infection is more likely to be correctly identified among women who are cultured two times than among those who are cultured only once. By using only the first culture we have ensured that infection was identified on the basis of the same number of cultures, whether women were delivered of low- or normal–birth-weight infants.

Table 5.—Incidence and Relative Risk of Preterm and Term Low Birth Weight Associated With Infection at Enrollment*

Infection Status	Incidence Low Birth Weight		
	Preterm	Term	Total†
Mycoplasma hominis			
Positive, %	4.7 (16/343)	3.5 (12/343)	**8.2 (28/343)**
Negative, %	1.6 (7/453)	2.9 (13/453)	**4.4 (20/453)**
RR (95% CI)‡	3.0 (1.3-6.9)	1.2 (0.6-2.6)	. . .
Chlamydia trachomatis			
Positive, %	5.1 (7/138)	2.9 (4/138)	**8.0 (11/138)**
Negative, %	2.5 (16/635)	3.3 (21/635)	**5.8 (37/635)**
RR (95% CI)†	2.0 (0.9-4.8)	0.9 (0.3-2.5)	. . .
Ureaplasma urealyticum			
Positive, %	3.1 (17/546)	3.5 (19/546)	**6.6 (36/546)**
Negative, %	2.4 (6/247)	2.4 (6/247)	**4.9 (12/247)**
RR (95% CI)‡	1.3 (0.5-3.2)	1.4 (0.6-3.5)	. . .

*Gestation at enrollment less than 24 weeks.
†Term and preterm, excluding those lacking delivery gestation data.
‡RR indicates relative risk, ratio of incidence of outcome among women with positive cultures to incidence among women with negative cultures, 95% confidence intervals (CI).

RESULTS

The women enrolled at the two sites were similar in demographic characteristics, although the women who enrolled at Gallup (n = 949) obtained initial prenatal care later in gestation ($P<.01$) than did the women at Crownpoint (n = 254). Overall, 23% of the women enrolled were younger than 20 years, 34% were nulliparous, 45% sought prenatal care in the first trimester, 44% in the second. Fifty percent of the women had graduated from high school (Table 1). The pregnancy outcomes of 1100 (91%) were known (1041 were delivered of single infants).

The demographic characteristics of the 104 women unavailable for follow-up were similar to those who were delivered of single infants, although women in the former group were somewhat more educated and had obtained initial prenatal care earlier than women in the latter group.

Characteristics of Those Infected

Women were considered to be infected with an organism if a cervical culture on either visit was positive. The prevalences of the three infections were *M hominis*, 50% (586/1163); *C trachomatis*, 22% (251/1152); and *U urealyticum*, 81% (944/1163). The infections were more prevalent among younger, less educated, nulliparous women and among those with a history of gonorrhea. The factor most strongly associated with being infected with one organism was the presence of either of the other two organisms (Table 2).

Low Birth Weight

The overall incidence of low–birth-weight infants among women who enrolled in prenatal care by 24 weeks' gestation and who were delivered of a single infant was 6.2% (55/892) (Table 3). The relative risk (RR) for the delivery of a low–birth-weight infant associated with *M hominis* infection was 1.8 ($P<.05$); the RRs associated with *C trachomatis* (1.5) and with *U urealyticum* (1.3) were less and not significant. (The power of the study at $\alpha = 0.05$ to identify a twofold increase in the risk of low birth weight associated with *C trachomatis* was 0.69, and with *U urealyticum*, 0.78.)

The risks for low birth weight, associated with *C trachomatis* or *U urealyticum*, determined by logistic regression (odds ratios, 1.1 and 1.4, respectively; $P>.5$ for both) were similar to unadjusted results. However, the analysis of the risks associated with *M hominis* revealed a significant interaction between *M hominis* infection and a history of spontaneous abortion. The risk of low birth weight associated with *M hominis* among women without a history of spontaneous abortion was not significantly increased (odds ratio, 1.4).

Table 6.—Effects on Mean Birth Weight Associated With *Mycoplasma hominis* or *Chlamydia trachomatis* Infection at Enrollment

Analysis	*M hominis* Effect on Mean Birth Weight, g*	*M hominis* P	*C trachomatis* Effect on Mean Birth Weight, g*	*C trachomatis* P
Unadjusted†	−103	<.01	−98	.02
Adjusted‡				
All gestations	−101	01	−52	NS
≥40 wk gestational age	−46	NS	−31	NS

*Difference between mean birth weight of infants born to mothers with the infection and that of infants whose mothers were not infected.
†The number of women evaluated for effect of *M hominis* was 920; and for *C trachomatis*, 896 women.
‡Controlling by multiple linear regression for parity, maternal height, weight, marital status, age, enrollment, gestation, and either *M hominis* or *C trachomatis* infections. For all gestations the number of women was 749; for 40 weeks' or greater gestational age, 416 women.

Table 7.—Risk Factors for Postpartum Endometritis (PPE)

Risk Factor	Incidence of Risk Factor,%*	Incidence of PPE, %†	RR‡	P
Cesarean section	16	9.4	2.6	.001
Age <20 y	23	7.1	2.0	.02
Nulliparity	34	6.6	1.9	.02
Labor >6 h	64	5.2	2.1	.04
PROM§	8	9.4	2.3	NS
Preterm <37 wk	6	9.3	1.9	NS
ROM >6 h§	19	6.4	1.6	NS
Vaginal examinations >4	46	5.4	1.5	NS

*Percent of women delivered of single infants, with the risk factor.
†Incidence of postpartum endometritis among women with the risk factor. Overall incidence is 4.5% (46/1026).
‡RR indicates relative risk, ratio of incidence of PPE among women with the risk factor to incidence among women without the factor.
§PROM indicates premature rupture of membranes; ROM, duration from membrane rupture to delivery.

Table 8.—Association of Postpartum Endometritis (PPE) With Infections

Infection Status*	Incidence of PPE, %†	RR (95% CI)‡	Odds Ratio§ (95% CI)
Mycoplasma hominis			
Positive	5.6 (28/504)	1.7 (0.9-3.1)	1.1 (0.5-2.2)‖ 4.7 (1.2-18.2)¶
Negative	3.3 (16/491)	. . .	. . .
Chlamydia trachomatis			
Positive	5.0 (11/218)	1.3 (0.7-2.5)	1.2 (0.6-2.6)
Negative	3.9 (30/770)	. . .	. . .
Ureaplasma urealyticum			
Positive	4.8 (39/821)	1.7 (0.7-4.1)	1.3 (0.5-3.5)
Negative	2.9 (5/174)	. . .	. . .

*The number of women whose *M hominis* was unknown was 31; for *C trachomatis*, 38 women; and for *U urealyticum*, 31 women.
†The overall incidence of PPE was 4.5% (46/1026).
‡RR indicates relative risk, ratio of incidence of endometritis among positive cultures to incidence among negative cultures, 95% confidence intervals (CI).
§Odds ratio is determined by logistic regression, controlling for premature rupture of membranes, cesarean section, age, nulliparity, and coexisting infection.
‖Indicates vaginal delivery.
¶Indicates cesarean section.

However, among those with a history of spontaneous abortion, the presence of *M hominis* was associated with a significantly elevated odds ratio for low birth weight of 9.4 (Table 4).

Among women having a history of spontaneous abortion, eight (11.3%) low–birth-weight infants were born to the subgroup of *M hominis*–infected women (n=71); one low–birth-weight infant (1.0%) was born among the *M hominis*–negative women (n=105) (unadjusted RR, 11.8). Among those without a history of spontaneous abortion, 19 infants of low birth weight (5.4%) were born to the *M hominis*–negative women (n=355), and 20 (7.3%) were born to *M hominis*–infected women (n=273) (RR, 1.4).

We next categorized low–birth-weight infants as term (≥37 weeks' gestation) or preterm (<37 weeks' gestation) (Table 5). The association of *M hominis* with low birth weight is the result of a significantly increased risk of preterm low birth weight (RR, 3.0; $P=.01$); for term low birth weight, the association was not significant. The other infections are also associated with increased rates of preterm low birth weight, but the magnitude of the risks is less and not significant. Neither premature rupture of membranes nor spontaneous labor was predominantly responsible for the increase in preterm low birth weight among *M hominis*–infected women; there were proportional increases in both these categories of preterm deliveries.

Mean Birth Weight

Women with either *M hominis* or *C trachomatis* infection (based on culture results from the initial visit) were delivered of infants whose mean birth weight was significantly less than that of infants whose mothers were not infected with those organisms. Analysis by multiple linear regression, controlling for confounding variables, confirmed that *M hominis* infection was associated with significantly lower mean birth weight; *C trachomatis* infection was not associated with a significant effect. The same technique was used to assess the effect associated with *M hominis* or *C trachomatis* infections on mean birth weight of infants born after at least 40 weeks' gestation. In this group, differences in length of gestation should not result in differences in birth weight. The differences in mean birth weight associated with *M hominis* or *C trachomatis* infections (46 and 31 g, respectively) were minimal and not significant (Table 6).

Postpartum Morbidity

Postpartum endometritis occurred among 46 women. Associations (though not all were significant) were found between postpartum endometritis and recognized risk factors[23] (Table 7). Analysis by logistic regression revealed that *M hominis* infection was associated with postpartum endometritis among women undergoing cesarean section. *Mycoplasma hominis* infection did not contribute to the risk of endometritis among women with vaginal deliveries (Table 8). Fifteen cases of endometritis occurred among women undergoing a cesarean section (n=160)—11 among *M hominis*–infected women (n=75), and three among *M hominis*–negative women (n=79). (One case occurred among six women whose *M hominis* status was unknown.)

Previous work had identified association between cervical infection and the

Table 9.—Association of Postpartum Endometritis/Fever (PPE/F) With Infections

Infection Status*	Incidence PPE/F, %†	RR (95% CI)‡	Odds Ratio (95% CI)§
Mycoplasma hominis			
Positive	11.2 (57/509)	1.2 (0.8-1.7)	1.2 (0.8-1.9)
Negative	9.4 (47/500)	. . .	. . .
Chlamydia trachomatis			
Positive	10.4 (23/222)	1.1 (0.7-1.6)	1.2 (0.7-2.0)
Negative	9.9 (77/780)	. . .	. . .
Ureaplasma urealyticum			
Positive	10.8 (90/833)	1.4 (0.8-2.3)	1.2 (0.6-2.2)
Negative	8.0 (14/176)	. . .	. . .

*The number of women whose *M hominis* status was unknown was 26; for *C trachomatis*, 33 women; and for *U urealyticum*, 26 women.

†The overall incidence of PPE/F was 10.6% (110/1035).

‡Unadjusted relative risk (RR) indicates ratio of incidence of PPE/F among positive cultures to incidence among negative cultures, with 95% confidence intervals (CI).

§Adjusted odds ratio is determined by logistic regression controlling for parity, cesarean section, gestation less than 37 weeks, greater than six hours of labor, zero hours of labor, duration of membrane rupture less than six hours, age younger than 20 years, number of vaginal examinations, premature rupture of membranes, and coexisting infection.

occurrence of postpartum morbidity, defined as either postpartum endometritis or postpartum fever (see "Methods" section). However, although we found an association as noted above with endometritis, an association was not found when we broadened the definition of postpartum morbidity to include postpartum fever (Table 9).

Serological Data

Among those women enrolled in the study and found to have *C trachomatis* on either culture (n = 251), 89% (181/204) had a positive IgG titer in either of the two serum specimens; only 5% (10/204) had a positive IgM titer.

The serological subgroups of *C trachomatis*–infected women, excluding those who had a spontaneous abortion, whose pregnancy outcomes were known were as follows: (1) recent infection (n = 16); (2) chronic infection (n = 133); and (3) unclassifiable (n = 71). The women whose *C trachomatis* infections were acquired recently were delivered of three infants (19%) of low birth weight (one was stillborn); women with chronic *C trachomatis* infection were delivered of six such infants (4.5%) (RR, 4.2; $P = .06$; by two-tail Fisher's exact test). The six women with unclassifiable infection were delivered of infants weighing less than 2500 g (8.5%).

Therefore, although we found that most *C trachomatis* infections were chronic, the few women we classified as having recent *C trachomatis* infection were at increased risk for the delivery of a low–birth-weight infant.

COMMENT

This study has demonstrated that, among Navajo women, endocervical culture can identify populations at risk for two important pregnancy outcomes. We have shown that *M hominis* was associated with the delivery of low–birth-weight infants among women with a history of spontaneous abortion and associated with postpartum endometritis among women undergoing cesarean section. However, the true magnitude of the association between *M hominis* and the delivery of low–birth-weight infants among women with prior spontaneous abortion is uncertain. The calculated odds ratio of 9.4 is certainly an overestimate. (This odds ratio represents a comparison between the rate of low birth weight among *M hominis*–positive women who have a history of spontaneous abortion and the rate of low birth weight among *M hominis*–negative women with a similar history. This latter group experienced an unrealistically low rate of low birth weight of 1%.) These associations persisted after controlling for important risk factors and for the presence of *C trachomatis* or *U urealyticum*. (One important risk factor for low birth weight not controlled for was smoking during pregnancy. However, it is unlikely that our results would be altered by such a consideration since less than 5% of Navajo women smoke during pregnancy [Carol Milligan, CNM, oral communication, March 1986].) In addition, the increased risk of low birth weight was associated with preterm, not term, delivery.

It is unclear why these populations are at risk. Possibly, in women with a history of spontaneous abortion, the cervical mucous plug does not function adequately, and allows ascending infection; another possibility is that prior loss may have occurred as a result of *M hominis* infection—an infection that then persisted until the study pregnancy. Obviously, this association of *M hominis* and prior spontaneous abortion with low birth weight must be corroborated in other studies before it is appropriate to recommend that pregnant women be screened for *M hominis*, regardless of history of pregnancy loss.

The association of *M hominis* with postpartum endometritis among women undergoing cesarean section suggests that surgical insult is necessary to allow *M hominis* to become invasive. However, no association was found between *M hominis* and postpartum morbidity, broadly defined as postpartum fever or endometritis—although an association was noted previously.[11] In that study such postpartum morbidity complicated 2.9% of deliveries; in our population, it occurred following 10.3% of births. It is possible that this threefold difference in incidence may reflect the contribution of other risk factors that were not controlled for—factors that may have obscured the association.

These associations—and the risks of adverse outcome—may need to be considered in the context of a woman's immune response to the infection. Earlier work has suggested that the appearance during pregnancy of organism-specific IgM or of a fourfold titer rise in organism-specific antibody may highlight subgroups of infected women at particular risk for adverse pregnancy outcome.[13,24] Such a response may identify recently acquired, or possibly invasive, infections. More chronic, less invasive infection may be associated with lower risks. In the population we studied, the great majority of *C trachomatis* infections were apparently chronic. Interestingly, the overall prevalence of all three infections was very high—as high as reported in any population[25]—and cervical infection was still very prevalent among older (>29 years) women. This suggests that infection may persist for prolonged periods, or that exposure to the infections is ongoing and that prior exposure, and presumably antibody, does not prevent reacquisition of lower tract infection (but may protect against invasion).

Although we have no serological data concerning *M hominis* infections, our study has demonstrated that most *C trachomatis* infections in this population were chronic. Almost 90% of the *C trachomatis*–infected population had anti–*C trachomatis* IgG present in serum and less than 5% had anti-*C trachomatis* IgM (a correlate of recent infection). This may explain why we found no association between cervical *C trachomatis* infection and either low birth weight or postpartum endometritis. It is possible that nearly all the *C trachomatis*–infected women were manifesting chronic local infection and were not susceptible to invasive *C trachomatis* infection, and furthermore,

that only invasive infection leads to endometritis or low–birth-weight delivery. Our data do suggest that women recently infected with *C trachomatis* may be at risk, but the percentage of such women in this population was probably small—about 10% (although almost 30% of *C trachomatis*–infected women were unclassifiable). The public health utility of attempting to identify this subgroup is not clear.

This study failed to demonstrate associations between low birth weight and genital infections with either *C trachomatis* or *U urealyticum*—results consistent with some studies[10,11] but not with others.[5,26] Such inconsistencies may have occurred for reasons mentioned earlier—differences in study design or differences in the proportion of *C trachomatis* or *U urealyticum* infections that were chronic in the populations studied. It is possible that our findings among Navajos cannot be generalized to other populations. However, a pathophysiologic effect of cervical infections should not be population dependent. Furthermore, it is reassuring that similar results were found in a study employing similar laboratory facilities and similar study design, but which evaluated an entirely different population.[11]

It is unlikely that the failure to identify pregnancy outcomes of 9% of the enrollees was responsible for inconsistent results. The Gallup facility is the regional center. Women from Crownpoint who had complications were cared for at Gallup, and women from Gallup were rarely, if ever, transferred elsewhere. Most of the women who were unavailable for follow-up moved or received care at other facilities. In addition, in terms of age, parity, enrollment gestation, and education, women unavailable for follow-up were at no greater risk for a low–birth-weight delivery than the women giving birth to single infants; likewise, among women unavailable for follow-up, the prevalence of *M hominis*, *U urealyticum*, or *C trachomatis* infection (42.6%, 69.2%, and 18.7%) was very similar to that among the mothers of single infants (42.7%, 69.5%, and 17.4%).

Although adverse outcomes were associated with *M hominis* infection, it is unclear what the appropriate treatment for *M hominis* is or if *M hominis* is indeed the causal agent associated with these adverse events. Both *Bacteroides* infection and bacterial vaginosis—conditions each highly correlated with *M hominis* infection[27]—have also been associated with adverse pregnancy outcomes.[9,28] It may be that *M hominis* infection is a marker for the presence of the causative organism.

In summary, we have found that *M hominis*, but not *C trachomatis* or *U urealyticum*, was related to low birth weight and postpartum endometritis. In addition, we identified subpopulations at particular risk for these outcomes. The association with low birth weight reflects an increase in preterm low birth weight, but not term low birth weight, and our results suggest that women with a history of abortion are at greatest risk. Similarly, women undergoing cesarean section constitute a subgroup whose risk of endometritis is increased by *M hominis* infection.

Although recently acquired *C trachomatis* infection appears to increase the risk of low birth weight, the percentage of patients with such infection in the study population, and probably in most populations, was small. Notwithstanding the size of the subgroup at risk, it does appear that *C trachomatis* infection is a preventable cause of low birth weight. However, *C trachomatis* infection in most women was chronic and our results suggest that the course of their pregnancies was not adversely affected by such infection.

The use of serological tests to classify *M hominis* infections in a similar manner may further clarify the relationship between *M hominis* and pregnancy complications. In the meantime, we believe this study provides strong evidence that *M hominis* and, probably, *C trachomatis* infections are indeed associated with adverse pregnancy outcomes and that there are specific, identifiable subpopulations at risk.

This investigation was supported in part by grant AI 17688 from the Thrasher Research Fund and by grant AI 17688 from the National Institutes of Health. Dr Harrison was the recipient of a John A. and George L. Hartford Fellowship.

References

1. McCormick MC: The contribution of low birthweight to infant and childhood morbidity. *N Engl J Med* 1985;312:82-90.
2. Elder HA, Santamarina BAG, Smith S, et al: The natural history of asymptomatic bacteriuria during pregnancy: The effect of tetracyline on the clinical course and the outcome of pregnancy. *Am J Obstet Gynecol* 1971;111:441-462.
3. Cassell GH, Cole BC: Mycoplasmas as agents of human disease. *N Engl J Med* 1981;304:80-89.
4. Alexander ER, Harrison HR: Role of *Chlamydia trachomatis* in perinatal infection. *Rev Infect Dis* 1983;5:713-719.
5. Martin DH, Koutsky L, Eschenbach DA, et al: Prematurity and perinatal mortality in pregnancies complicated by maternal *Chlamydia trachomatis* infections. *JAMA* 1982;247:1585-1588.
6. Braun P, Lee YH, Klein JO, et al: Birth weight and genital mycoplasmas in pregnancy. *N Engl J Med* 1971;284:167-170.
7. Kundsin RB, Driscoll SG, Monson RR, et al: Association of *Ureaplasma urealyticum* in the placenta with perinatal morbidity and mortality. *N Engl J Med* 1984;310:941-945.
8. Wager GP, Martin DH, Koutsky L, et al: Puerperal infectious morbidity: Relationship to route of delivery and to antepartum *Chlamydia trachomatis* infection. *Am J Obstet Gynecol* 1980;138:1028-1033.
9. Gravett MG, Nelson HP, DeRouen T, et al: Independent associations of bacterial vaginosis and *Chlamydia trachomatis* with adverse pregnancy outcome. *JAMA* 1986;256:1899-1903.
10. Ross JM, Furr PM, Taylor-Robinson D, et al: The effect of genital mycoplasmas on human fetal growth. *Br J Obstet Gynaecol* 1981;88:749-755.
11. Harrison HR, Alexander ER, Weinstein L, et al: Cervical *Chlamydia trachomatis* and mycoplasmal infections in pregnancy: epidemiology and outcomes. *JAMA* 1983;250:1721-1727.
12. Munday PE, Porter R, Falder PF, et al: Spontaneous abortion: An infectious aetiology? *Br J Obstet Gynaecol* 1984;91:1177-1180.
13. Harrison HR: Prospective studies of *Mycoplasma hominis* infection in pregnancy. *Sex Transm Dis* 1983;10:311-317.
14. Edelman R: Summary of a workshop on maternal genitourinary infections and the outcome of pregnancy. *J Infect Dis* 1983;147:596-605.
15. Wentworth BB, Alexander ER: Isolation of *Chlamydia trachomatis* by use of 5-iodo-2-deoxyuridine-treated cells. *Appl Microbiol* 1974;27:912-916.
16. Kenny GE: Mycoplasmata, in Lenette EH, Balows A, Hansler WJ, et al (eds): *Manual of Clinical Microbiology*. Washington, DC, American Society for Microbiology, 1980, pp 365-370.
17. Yoder BL, Stamm WE, Koester CM, et al: A microtest procedure for isolation of *C trachomatis*. *J Clin Microbiol* 1981;13:1036-1039.
18. Wang SP, Grayston JT, Alexander ER, et al: Simplified microimmunofluorescence test with trachoma-lymphogranuloma venereum (*Chlamydia trachomatis*) antigens for use as a screening test for antibody. *J Clin Microbiol* 1975;1:250-255.
19. Rothman KJ, Boice JD: Epidemiologic analysis with a programmable calculator. National Institutes of Health Publication 79-1649. US Dept of Health, Education, and Welfare, 1979.
20. Cox DR: Analysis of binary data, in *Methuen's Monographs on Applied Probability and Statistics*. London, Methuen & Co, 1970.
21. Kleinbaum DG, Kupper LL, Morgenstern H: Modeling: Analysis strategy, in *Epidemiologic Research*. Belmont, Calif, Lifetime Learning Publications, 1982, pp 447-456.
22. Schachter J. Biology of *Chlamydia trachomatis*, in Holmes KK, Mardh P-A, Sparling PF, Wiesner PJ (eds): *Sexually Transmitted Diseases*. McGraw-Hill International Book Co, 1984, p 252.
23. Eschenbach DA: New concepts of obstetric and gynecologic infection. *Arch Intern Med* 1982;142:2039-2044.
24. Kass EH, McCormack WM, Lin JS, et al: Genital mycoplasmas as a cause of excess premature delivery. *Trans Assoc Am Phys* 1981;94:261-266.
25. Harrison HR, Boyce WT, Haffner HJ, et al: The prevalence of genital *Chlamydia trachomatis* and mycoplasmal infections during pregnancy in an American Indian population. *Sex Transm Dis* 1983;10:184-186.
26. Klein JO, Buckland D, Finland M: Colonization of newborn infants by mycoplasmas. *N Engl J Med* 1969;280:1025-1030.
27. Koutsky LA, Stamm WE, Brunham RC, et al: Persistence of *Mycoplasma hominis* after therapy: Importance of tetracycline resistance and of coexisting vaginal flora. *Sex Transm Dis* 1983;10(suppl 4):374-381.
28. Minkoff H, Grunebaum AN, Schwarz RH, et al: Risk factors for prematurity and premature rupture of membranes: A prospective study of the vaginal flora in pregnancy. *Am J Obstet Gynecol* 1984;150:965-972.