JOURNAL OF CLINICAL MICROBIOLOGY, Jan. 2006, p. 51–55 Vol. 44, No. 1
0095-1137/06/$08.00+0 doi:10.1128/JCM.44.1.51–55.2006

Association between Preterm Birth and Vaginal Colonization by Mycoplasmas in Early Pregnancy

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Received 10 June 2005/Returned for modification 29 June 2005/Accepted 28 September 2005

To examine the association between colonization by two newly classified species of genital ureaplasmas (*Ureaplasma parvum* and *U. urealyticum*) in early pregnancy and subsequent late abortion or preterm birth at <34 weeks of gestation, four species of genital mycoplasmas—*Mycoplasma genitalium*, *M. hominis*, *U. parvum*, and *U. urealyticum*—as well as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* were examined by PCR-based methods in a prospective cohort study of 877 women with singleton pregnancies at <11 weeks of gestation. Antibiotics were used only in cases in which *C. trachomatis* and/or *N. gonorrhoeae* was detected. Multivariate logistic-regression analysis was used to assess independent risk factors after taking maternal low body weight and past history of preterm birth into account. *M. genitalium*, *M. hominis*, *U. parvum*, *U. urealyticum*, *C. trachomatis*, and *N. gonorrhoeae* were detected in 0.8%, 11.2%, 52.0%, 8.7%, 3.2%, and 0.1% of these 877 women, respectively. Twenty-one (2.4%) women experienced late abortion or preterm birth at <34 weeks of gestation. Three factors—detection of *U. parvum* in the vagina (odds ratio [OR], 3.0; 95% confidence interval [CI], 1.1 to 8.5); use of antibiotics, such as penicillin and cefatrizine, for incidental inflammatory complications before 22 weeks of gestation (OR, 4.2; 95% CI, 1.6 to 10.0); and past history of preterm birth (OR, 10.4; 95% CI, 2.7 to 40.5)—were independently associated with late abortion and preterm birth. In conclusion, vaginal colonization with *U. parvum*, but not *U. urealyticum*, is associated with late abortion or early preterm birth.

Preterm birth and low birth weight are the leading causes of neonatal mortality and morbidity in the developed world. More than 60% of the mortality among infants without anatomic or chromosomal defects can be attributed to low birth weight (20). Ascending genital tract infections contribute to up to 50% of premature deliveries, particularly those occurring before 30 weeks of gestation (4, 15). Moreover, the rate of neonatal complications has been shown to be higher in neonates born to women with microbial invasion of the amniotic cavity than born to those women without infection (10).

Genital mycoplasmas, including *Mycoplasma hominis*, *M. genitalium*, and *Ureaplasma* spp., are suspected of contributing to a number of pathological conditions. *M. hominis* was isolated from the amniotic fluid in 30% of 404 women with intraamniotic infection (21) and was shown to be associated with preterm birth at <33 weeks of gestation (23). *M. genitalium* was suggested to cause urethritis in men (11) and mucopurulent cervicitis in women (16), but its association with preterm birth has not been studied extensively. *Ureaplasma* has been implicated in infertility, spontaneous abortion, stillbirth, premature birth, low birth weight, and perinatal morbidity and mortality (3). Vaginal colonization with *Ureaplasma* has not been associated with preterm birth (3), while the presence of *Ureaplasma* in the amniotic fluid is associated with a robust host response in fetal, amniotic, and maternal compartments (24) and subsequent preterm birth (7). It is not known why this microorganism invades the amniotic cavity only in some women despite heavy colonization of the vagina by *Ureaplasma*.

Recently, the species previously classified as *Ureaplasma urealyticum* was separated into two new species: *U. parvum* (previously *U. urealyticum* biovar 1) and *U. urealyticum* (previously *U. urealyticum* biovar 2) (14, 19). Therefore, *U. urealyticum* organisms examined in previous studies (3, 7, 24) may have included both *U. parvum* and emended *U. urealyticum.* It is possible that the two new *Ureaplasma* species differ from each other in pathogenicity, as suggested in several studies (1, 18).

The purpose of the present prospective study was to examine the relationship between preterm birth and vaginal colonization with these four species of mycoplasmas in early pregnancy.

MATERIALS AND METHODS

Subjects and sample collection. A total of 1,040 women with singleton pregnancies at <11 weeks of gestation were enrolled from Hokkaido University Hospital and nine affiliated hospitals after their fetuses were confirmed to have normal heartbeats between January 2002 and December 2002. A clean, unlubricated speculum was placed into the vagina. Sterile cotton swabs were used to obtain vaginal material from the posterior vaginal fornix. All the swab specimens obtained from pregnant women were subjected to alkaline denaturation.

Hybrid Capture test and PCR microtiter plate hybridization. Alkaline-denatured samples were first subjected to both the Hybrid Capture 2 CT-ID test and the GC-ID test (Digene Corporation, Gaithersburg, MD) for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, respectively, in accordance with the manufacturer's instructions. DNA was extracted from the remainder of these alkaline-denatured samples. The DNA extracts were examined for four species of mycoplasmas (*M. genitalium*, *M. hominis*, *U. parvum*, and emended *U. urealyticum*) by using the mycoplasma species-specific PCR-microtiter plate hybridization assay of Yoshida et al. (25). Briefly, PCR was performed for the 16S rRNA gene by using primer pairs for both mycoplasmas and ureaplasmas. The amplified products were detected by hybridization with mycoplasma species-specific oligonucleotide probes immobilized on microtiter plates (25).

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TABLE 1. Clinical profiles and outcomes

Characteristic	Mean ± SD (%) for:			P^a
	Total	Preterm birth group	Control group	
No. of women	877	21	856	
Age (yr)	28.9 ± 4.6	29.6 ± 6.1	28.9 ± 4.5	0.500
No. with age of <25 yr	147 (16.8)	4 (19.0)	143 (16.7)	0.999
Gestation wk at entry	8.6 ± 1.1	8.8 ± 1.4	8.6 ± 1.1	0.348
Nulliparous	482 (55.0)	14 (66.7)	468 (54.7)	0.375
BMI at entry of <19.8[b]	347 (39.6)	5 (23.8)	342 (40.0)	0.176
Past history of preterm birth	18 (2.1)	3 (14.3)	15 (1.8)	0.007
Antibiotic use at <22 wk for:				
C. trachomatis	28 (3.2)	0 (0.0)	28 (3.3)	0.999
Other reasons	102 (11.6)	7 (33.3)	95 (11.1)	0.006
Cervical cerclage	19 (2.2)	1 (4.8)	18 (2.1)	0.372
Vaginal colonization with:				
M. genitalium	7 (0.8)	0 (0.0)	7 (0.8)	0.999
M. hominis	98 (11.2)	4 (19.0)	94 (11.0)	0.280
U. parvum	456 (52.0)	16 (76.2)	440 (51.4)	0.027
U. urealyticum	76 (8.7)	1 (4.8)	75 (8.8)	0.999
Any species of mycoplasma	564 (64.3)	19 (90.5)	545 (63.7)	0.010
More than one mycoplasma species	70 (8.0)	2 (9.5)	68 (7.9)	0.681
C. trachomatis and any species of mycoplasma	22 (2.5)	0 (0.0)	22 (2.6)	0.999
C. trachomatis	28 (3.2)	0 (0.0)	28 (3.3)	0.999
N. gonorrhoeae	1 (0.1)	0 (0.0)	1 (0.1)	0.999

[a] Comparison between the preterm birth and control groups.
[b] BMI = body weight/body height squared (kg/m^2).

Antibiotics. Antibiotics were administered to women in whom *C. trachomatis* and/or *N. gonorrhoeae* was detected but not to those in whom any mycoplasma was detected in the absence of *C. trachomatis* or *N. gonorrhoeae*.

Clinical profile and pregnancy outcome. Gestational age was determined by a combination of the last menstrual period and ultrasonographic evaluation. Data regarding age, parity, body mass index (BMI), previous obstetric history related to preterm labor, use of antibiotics, and gestational week at delivery were obtained from the medical charts.

Informed consent. This study was approved by each hospital's ethics committee, and all women gave written informed consent prior to participation.

Statistical analyses. The Mann-Whitney U test, Fisher's exact probability test, and multivariate logistic-regression analysis (SPSS; SPSS Inc., Chicago, IL) were used for statistical analyses, with a P of <0.05 considered statistically significant.

RESULTS

A total of 877 women were analyzed in the present study after 163 women were excluded for the following reasons: induced abortion (n = 12), spontaneous preterm delivery due to a major anomaly of the fetus incompatible with life (n = 2), induced preterm delivery because of maternal breast cancer (n = 1), and unavailability for follow-up (n = 148).

The pregnancies of 21 (2.4%) of the 877 women ended in spontaneous abortion or preterm birth at <34 weeks of gestation (preterm birth group) (Table 1). Five of these 21 women experienced miscarriage between 11 and 15 weeks of gestation (Table 2). One woman experienced intrauterine fetal death at 24 weeks of gestation. Causes of preterm birth for the remaining 15 women were premature rupture of the membranes in 7 women at 26 to 33 weeks of gestation, failure to suppress uterine activity in 5 women at 28 to 33 weeks of gestation, preeclampsia in 1 woman at 30 weeks of gestation, fetal growth restriction in 1 woman at 30 weeks of gestation, and intrauterine infection in 1 woman at 32 weeks of gestation (Table 2). The 856 women who gave birth at or beyond 34 weeks of gestation served as a control group (Table 1).

There were no significant differences in mean maternal age, number of women aged <25 years, number of nulliparous women, number of women with BMI of <19.8, or number of women who had cervical cerclage in the current pregnancy between the two groups divided by the length of gestation (Table 1). A significantly larger number of women had a past

TABLE 2. Bacterial characteristics and cause of early delivery for the preterm birth group

Patient	Gestational wk at delivery	Presence of[b]:				Cause of preterm delivery[a]
		M. genitalium	*M. hominis*	*U. parvum*	*U. urealyticum*	
1	11	−	−	−	−	Miscarriage
2	11	−	−	+	−	Miscarriage
3	12	−	−	+	−	Miscarriage
4	13	−	−	−	+	Miscarriage
5	15	−	−	+	−	Miscarriage
6	24	−	−	+	−	Fetal death
7	26	−	−	+	−	PROM
8	27	−	−	+	−	PROM
9	28	−	+	−	−	FSUA
10	29	−	−	+	−	PROM
11	30	−	−	+	−	PROM
12	30	−	+	+	−	Fetal growth restriction
13	30	−	−	+	−	Preeclampsia
14	31	−	−	+	−	PROM
15	31	−	−	+	−	FSUA
16	31	−	−	−	−	FSUA
17	32	−	−	+	−	Intrauterine infection
18	32	−	+	+	−	FSUA
19	33	−	+	−	−	PROM
20	33	−	−	+	−	PROM
21	33	−	−	+	−	FSUA

[a] PROM, premature rupture of the membranes; FSUA, failure to suppress uterine activity.
[b] +, present; −, absent.

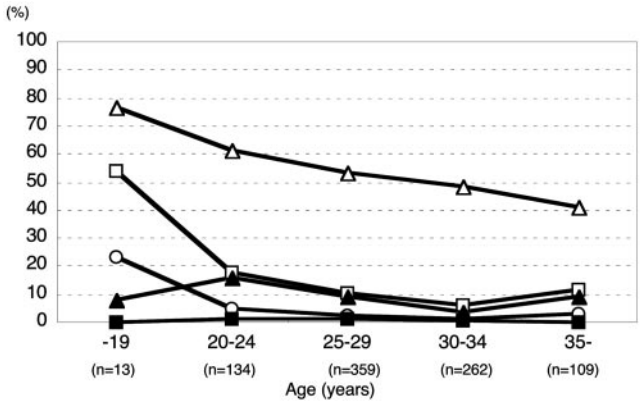

FIG. 1. Prevalence of vaginal mycoplasmas and *C. trachomatis* according to patient age. □, *M. hominis*; ■, *M. genitalium*; △, *U. parvum*; ▲, *U. urealyticum*; ○, *C. trachomatis*.

history of preterm birth at <37 weeks of gestation in the preterm birth group. Antibiotic use before 22 weeks of gestation was confirmed for a total of 130 women. Antibiotics, such as clarithromycin, were used to eradicate *C. trachomatis* in 28 women. All of the 28 women with vaginal colonization by *C. trachomatis* were treated with antibiotics and did not give birth at <34 weeks of gestation. Antibiotics, such as penicillin and cefatrizine, were used in the remaining 102 women before 22 weeks of gestation for several reasons, including upper respiratory tract infection in 66 women (3/21 [14.3%] for the preterm birth group versus 63/856 [7.4%] for the control group), prophylactically after genetic amniocentesis in 13 women (1/21 [4.8%] versus 12/856 [1.4%]), prophylactically after cervical suture in 12 women (1/21 [4.8%] versus 11/856 [1.3%]), enteritis in 3 women (1/21 versus 2/856), urinary tract infection in 3 women (0/21 versus 3/856), suspected intrauterine infection in 2 women (0/21 versus 2/856), parotitis in 1 woman (0/21 versus 1/856), *N. gonorrhoeae* in 1 woman (0/21 versus 1/856), and cervicitis in 1 woman (1/21 versus 0/856). Thus, the reasons for antibiotic use did not differ largely between the two groups. However, a significantly larger number of women were treated with antibiotics before 22 weeks of gestation in the preterm birth group than in the control group for reasons other than the presence of *C. trachomatis*.

M. genitalium, *M. hominis*, *U. parvum*, *U. urealyticum*, *C. trachomatis*, and *N. gonorrhoeae* were detected in 0.8%, 11.2%, 52.0%, 8.7%, 3.2%, and 0.1% of the 877 women, respectively (Table 1). Five hundred sixty-four women (64.3%) harbored mycoplasma species (any of the four species), and 70 women (8.0%) harbored combinations of more than one mycoplasma species. Younger pregnant women seemed to have higher frequencies of colonization by *U. parvum*, *M. hominis*, and *C. trachomatis* than did older women (Fig. 1). The prevalences of *M. genitalium*, *M. hominis*, *U. urealyticum*, and *C. trachomatis* did not differ between the two groups, while mycoplasma species and *U. parvum* were detected in a significantly larger number of women in the preterm birth group than in the control group (Table 1).

Among the 16 women with *U. parvum* in the preterm birth group, two were coinfected with *M. hominis* (Table 2). Six of seven women (85.7%) who experienced preterm premature rupture of the membranes harbored *U. parvum*. One woman with *U. urealyticum* in the preterm birth group did not harbor other mycoplasma species. Neither *C. trachomatis* nor *N. gonorrhoeae* was detected in this group (Table 1).

TABLE 3. Association of vaginal colonization by *C. trachomatis* with that by mycoplasmas

Mycoplasma	No. (%) of patients with mycoplasmal colonization when *C. trachomatis* is:		P^a
	Present (n = 28)	Absent (n = 849)	
M. genitalium	2 (7.1)	5 (0.6)	0.0187
M. hominis	7 (25.0)	91 (10.7)	0.0287
U. parvum	21 (75.0)	435 (51.2)	0.0195
U. urealyticum	3 (10.7)	73 (8.6)	0.7278

[a] Comparison between groups with and without the presence of *C. trachomatis*.

U. parvum and/or *U. urealyticum* were detected in 523 (59.6%) of the 877 women. Nine of the 456 women with *U. parvum* were coinfected with *U. urealyticum*. Thus, among the 523 women with *Ureaplasma* infection, 447 (85.5%), 67 (12.8%), and 9 (1.7%) had *U. parvum*, *U. urealyticum*, and both, respectively. In these three groups, 16 (3.6%) of 447, 1 (1.5%) of 67, and 0 of 9 women subsequently developed late abortion or preterm birth at <34 weeks of gestation, respectively. Of 456 women with *U. parvum* infection, 49 (10.7%) were coinfected with *M. hominis*, while 49 (11.6%) of 421 women without *U. parvum* were infected with *M. hominis*, suggesting that *M. hominis* infection was independent of *U. parvum* infection. However, women with vaginal *C. trachomatis* were significantly more likely to have vaginal mycoplasmas other than *U. urealyticum* (Table 3).

As past history of preterm birth at <37 weeks of gestation, antibiotic use for organisms other than *C. trachomatis* before 22 weeks of gestation, and vaginal colonization by *U. parvum* were possible candidate risk factors for late abortion or preterm birth (Table 1), these three factors were entered into the logistic-regression model to assess independent risk factors for late abortion or preterm birth at <34 weeks of gestation. All three factors remained independently associated with late abortion or preterm birth (Table 4).

DISCUSSION

Although our cohort was relatively small for analysis of the role of mycoplasmas in preterm birth, the results of this prospective study demonstrated that women with vaginal *U. parvum* infection but not *U. urealyticum* infection, were at in-

TABLE 4. Multivariate logistic-regression analysis for assessment of independent risk factors for late abortion or preterm birth at <34 weeks of gestation

Risk factor	β	P	OR (95% CI)[a]
Constant	−0.02		
U. parvum	1.11	0.035	3.04 (1.08–8.52)
Use of penicillin or cefatrizine at <22 wk	1.44	0.003	4.24 (1.63–10.00)
Past history of preterm birth	2.35	0.001	10.44 (2.69–40.49)

[a] OR, odds ratio; CI, confidence interval.

creased risk for late abortion or preterm birth at <34 weeks of gestation irrespective of past history of preterm birth, which is a well-known risk factor for preterm birth (2, 13). This was also confirmed in the present study. However, it is important to note that 440 of 456 women (96.5%) with *U. parvum* colonization gave birth to infants at or beyond 34 weeks of gestation.

Previous studies using methods that did not differentiate between *U. urealyticum* and *U. parvum* concluded that ureaplasmal colonization of the lower genital tract was not associated with adverse pregnancy outcome, while ureaplasmal infection of the chorioamnion was strongly associated with chorioamnionitis, preterm birth, and perinatal morbidity and mortality (3). There have been several previous studies of the association of the two *Ureaplasma* species with clinical disease and/or pregnancy outcome (1, 5, 9, 12, 18). Approximately 80% of *Ureaplasma* isolates from the vagina are *U. parvum*, while *U. urealyticum* is isolated less often, with frequencies ranging from only 7% to 30% (1, 6, 17, 18). Coinfection also occurs in some women (1, 17, 18), consistent with our results regarding distribution. Similarly, approximately 80% of *Ureaplasma* isolates from the amniotic fluid are *U. parvum*; *U. urealyticum* is isolated less often, with frequencies of approximately 20% (12, 17). These results suggest that vaginal *U. parvum* and *U. urealyticum* invade the amniotic cavity in equal frequencies.

Our results contradicted those of an earlier study (1) with regard to pregnancy outcome. Abele-Horn et al. (1) examined the association of vaginal colonization by *U. parvum* and *U. urealyticum* with pregnancy outcome in 174 women (148 with *U. parvum* and 26 with *U. urealyticum*) in whom *Ureaplasma* was isolated as the sole pathogenic microorganism. In their study, all specimens were collected after admission to hospital for delivery, and women colonized with vaginal *Escherichia coli* or other gram-negative bacteria, hemolytic streptococci, peptostreptococci, peptococci, *N. gonorrhoeae*, *Candida albicans*, *Trichomonas vaginalis*, *C. trachomatis*, *Bacteroides* spp., *M. hominis*, or *Gardnerella vaginalis* were excluded from the study population. Preterm birth was reported to occur more frequently in women with *U. urealyticum* than in those with *U. parvum* at <30 weeks of gestation (16/26 [62%] versus 24/148 [16%], respectively; $P < 0.001$) and at <37 weeks of gestation (20/26 [77%] versus 52/148 [35%], respectively; $P < 0.05$), suggesting that *U. urealyticum* has a more adverse effect on pregnancy outcome (1). In our prospective cohort study using a representative general population enrolled in early pregnancy, the pregnancies of 16 (3.6%) of 447 women with *U. parvum* and 1 (1.5%) of 67 women with *U. urealyticum* ended in late abortion or preterm birth at <34 weeks of gestation. Thus, our study population differed markedly from that examined by Abele-Horn et al. (1). Further, as we did not examine the presence or absence of bacterial vaginosis in our study population and because women with bacterial vaginosis may have been excluded in the study by Abele-Horn et al. (1), it is possible that other microorganisms not examined in this study were responsible for the conflicting results.

The association of vaginal *M. hominis* with preterm birth has been reported as positive in some studies (8, 23) but not in others (22). *M. hominis* was detected in 4 of 21 women (19.0%) in the preterm birth group and in 94 of 856 women (11.0%) in the control group and was not a risk factor for late abortion or preterm birth at <34 weeks of gestation in the present study. As vaginal colonization with *M. hominis* seemed to be independent of that with *U. parvum*, it is possible that *M. hominis* will become an independent risk factor for early preterm birth in future larger studies. Indeed, in our previous study (23), *M. hominis* was cultured from the vagina in 8 (6.8%) of 118 women, 7 (3.1%) of 224 women, and 47 (2.9%) of 1,616 women who gave birth at 22 to 32 weeks of gestation, at 33 to 36 weeks of gestation, and at or after 37 weeks of gestation, respectively, and was an independent risk factor for preterm birth at <33 weeks of gestation.

Effective antibiotics for *Ureaplasma* species, such as clarithromycin, were used in only 28 women with *C. trachomatis* infection. Twenty-one women with *U. parvum* who were coinfected with *C. trachomatis* (Table 3) did not develop late abortion or preterm birth at <34 weeks of gestation. Thus, among the 456 women with *U. parvum* infection, 0 of 21 (0.0%) women who were treated incidentally with effective antibiotics, versus 16 of 435 (3.7%) women who were not treated with effective antibiotics, developed late abortion or preterm birth at <34 weeks of gestation. Although these figures did not reach the level of significance, it is possible that antibiotics such as clarithromycin played a role in preventing late abortion or early preterm birth in these women infected with *U. parvum*. Further randomized and controlled studies are necessary to confirm this possibility.

Unexpectedly, the use of antibiotics that are not effective against mycoplasmas, such as penicillin and cefatrizine, was an independent risk factor for late abortion or early preterm birth in the present study. As the majority of women who were treated with these antibiotics were suffering from inflammatory diseases, it may be that these diseases that required antibiotic use, rather than the antibiotics themselves, were associated with late abortion or early preterm birth.

In conclusion, this prospective cohort study of women at an early stage of pregnancy and representative of the general population demonstrated that *U. parvum*, but not *U. urealyticum*, is an independent risk factor for late abortion or early preterm birth, apparently conflicting with the results of a previous study (1). Further studies are required to determine the reason for this discrepancy.

ACKNOWLEDGMENTS

We thank the physicians at Tenshi Hospital, Hokkaido Social Insurance Central General Hospital, Kushiro Red Cross Hospital, Oji General Hospital, Kucchan-Kosei General Hospital, Hakodate Central General Hospital, Bibai Rousai Hospital, Sapporo Toho Hospital, and Iwaki Maternity Clinic for enrolling pregnant women in this prospective study.

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