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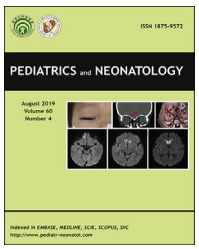

Original Article

Different degrees of maternal *Ureaplasma* colonization and its correlation with bronchopulmonary dysplasia in < 32 weeks' preterm infants

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Key Words
bronchopulmonary dysplasia;
colonization;
preterm infant;
ureaplasma species

Abstract *Background:* Ureaplasma spp. is a known risk factor for bronchopulmonary dysplasia (BPD). However, little is known about the effect of different degrees of maternal Ureaplasma colonization and their adverse outcomes. Hence, the aim of this study was to determine the effects of different degrees of maternal Ureaplasma colonization on BPD.
Methods: A retrospective cohort study of preterm infants delivered at <32 weeks' gestational age (GA) was performed. The infants were divided according to maternal Ureaplasma status as follows: high-colonization ($\geq 10^4$ CCU/ml, UUH), low-colonization ($<10^4$ CCU/ml, UUL), and noncolonization (controls). Subgroup analysis according to neonatal respiratory Ureaplasma (n-UU) was also performed to evaluate vertical transmission.
Results: In total, 245 infants were included in this study (UUH = 105, UUL = 47, controls = 93). The rates of preterm labor and histological chorioamnionitis were significantly different. The rate of BPD was significantly high in UUH ($P = 0.044$). The transmission rate of n-UU colonization was 36% in UUH and 32% in UUL ($P = 0.609$). The rate of BPD was 78% in n-UU (+) of UUH but 43% in n-UU (−) of UUL ($P = 0.027$).
Conclusions: High-degree colonization of maternal Ureaplasma was associated with preterm labor, histological chorioamnionitis, and neonatal BPD. The incidence of BPD was significantly higher in Ureaplasma-colonized infants born to women with high-degree colonization.

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1. Introduction

Bronchopulmonary dysplasia (BPD) remains a major cause of morbidity in premature infants, despite tremendous recent developments in the field of neonatal intensive care.[1,2] The etiology of BPD is multifactorial and includes hyperoxia, barotrauma, surfactant deficiency, nutritional deficiencies, fluid overload, patent ductus arteriosus (PDA), lung inflammation and infection.[2,3] Of these factors, prolonged exposure to inflammation initiated *in utero* by intrauterine infection in the immature lung during the saccular period plays a critical role in the development of BPD.[4]

Ureaplasma species constitute a group of microorganisms that are frequently isolated from amniotic fluid and infected placentas.[5,6] Although Ureaplasma is isolated from the vagina in 40%—80% of sexually active, asymptomatic women as a commensal organism, its presence is concerning because Ureaplasma can cause preterm delivery, spontaneous abortion or miscarriages, chorioamnionitis, neonatal morbidity, and perinatal death.[6,7]

Since 1988, when three independent groups first reported the association between Ureaplasma colonization of the lower respiratory tract in very preterm infants and the development of chronic lung disease, numerous studies on Ureaplasma colonization and BPD have been documented, with different results.[8—11] A recent meta-analysis demonstrated that the incidence of BPD in premature infants with Ureaplasma colonization in the respiratory tract was twice as high as the incidence in premature infants without colonization.[10]

Recently, as the density of information on the effects of Ureaplasma colonization on pregnancy outcomes has increased, Abele-Horn et al.[12] reported that the degree of vaginal Ureaplasma colonization was correlated with adverse pregnancy outcomes. However, clear evidence of a cause-and-effect relationship between maternal Ureaplasma colonization and neonatal BPD has not been reported, and controversies remain. Furthermore, studies of the effects of maternal high-density colonization versus low-density colonization on neonatal outcomes are rare.

Thus, the aim of this study was to determine the associations between different degrees of maternal Ureaplasma colonization and neonatal outcomes, particularly with respect to the development of BPD in premature infants.

2. Materials and methods

2.1. Study population

All singleton preterm infants born less than 32 weeks of gestational age (GA) who were admitted to the neonatal intensive care unit (NICU) of Hallym University Medical Center between January 2012 and December 2016 were included in this retrospective cohort study. Since high Ureaplasma concentrations in lung tissue can be identified between 22 and 32 weeks of gestation, we selected infants $<$32 weeks of GA as the study population.[13] Infants with congenital anomalies, including heart and pulmonary disorders (n = 9), those who were transferred to or from other institutes for any reason (n = 17), those with incomplete medical charts with no Ureaplasma results (n = 94), mothers with other bacterial co-infections, and twins or triplets (n = 194) were excluded.

Data collection was conducted retrospectively, and the institutional review boards of our facility allowed a waiver of informed consent for this retrospective chart review.

The study population was divided into three groups according to maternal Ureaplasma status as follows: high-colonization ($\geq 10^4$ CCU/ml, UUH), low-colonization ($<10^4$ CCU/ml, UUL), and controls, which were infants with no maternal Ureaplasma. Subgroup analysis according to neonatal respiratory Ureaplasma (n-UU) was also performed to evaluate vertical transmission. Various maternal and neonatal morbidities were compared.

2.2. Culture and polymerase chain reaction methods

As part of routine clinical practice in our institution, all women underwent a physical assessment, including a vaginal examination and vaginal swabs, on admission for delivery if preterm delivery was expected. Ureaplasma samples from the maternal lower genitalia area were obtained with vaginal swabs, and MYCOFAST® Evolution 2 (International Microbio, Signes, France) was used for culture analysis as a bedside procedure. This kit has a sensitivity and specificity of 95% and 98%, respectively. If the time interval between admission and delivery was more than one week in length, the microbiological examinations were repeated. To obtain a sufficient amount of sample, all procedures were performed twice. Only results without any co-existing pathogens, including hemolytic streptococci, *Mycoplasma hominis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and *Chlamydia trachomatis*, were recorded to exclude the influence of other co-infections. The Ureaplasma level was expressed quantitatively; high colonization was defined as a Ureaplasma colonization level of $\geq 10^4$ CCU/ml (UUH), and low colonization was defined as a Ureaplasma colonization level of $<10^4$ CCU/ml (UUL). We modified the definition of high and low colonization from Abele-Horn et al.[12]

For neonates, to determine the rate of vertical transmission to the respiratory tract and the effects of maternal Ureaplasma colonization, neonatal samples were collected from each infant using either tracheal aspiration (intubated infants) or nasopharyngeal swabs (nonintubated infants). These samples were obtained on days 1 and 3 after birth when the mother was confirmed to have Ureaplasma colonization and if both parents agreed. Real-time polymerase chain reaction was used to detect Ureaplasma colonization. DNA extraction was performed with a QIA amp viral RNA kit (Qiagen, Hilden, Germany) and the primers 14b (5′-CCAGGAAAACTACCAGGA-3′) and c72b (5′-CTCCTAATCTAACGA-3′).

2.3. Definitions of parameters

Infants were classified as 'preterm' if they were born before 37 weeks of gestation. Preterm labor was defined as regular uterine contractions (two or more in 10 min), despite treatment with tocolytic agents, which resulted in

preterm birth. Preterm premature rupture of membranes (PPROM) was defined as the rupture of membranes ≥24 h before delivery. Clinical chorioamnionitis (CC) was identified in the mother based on the presence of fever (≥37.8 °C) and two or more of the following: leukocytosis (≥15,000/μl), elevated C-reactive protein, foul odor, maternal tachycardia (>100 beats/minute), and/or fetal tachycardia (>160 beats/minute). Histological chorioamnionitis (HC) was defined as a placenta with polymorphonuclear leucocyte infiltration, as confirmed by a pathologist. Culture-proven sepsis was diagnosed based on a positive blood culture, along with demonstrated clinical signs. PDA with treatment was defined as the presence of PDA with medical treatment and/or surgical operation following confirmation by echocardiography. Abnormal brain sonogram was defined as abnormal sonography findings such as germinal matrix hemorrhage ≥ grade 3 and/or periventricular leukomalacia. BPD was diagnosed as a persisting requirement for oxygen supply for at least 28 days, and the BPD severity was classified as mild, moderate, or severe when oxygen dependency was present at 36 weeks of postmenstrual age (PMA), in accordance with the National Institutes of Health consensus definition.[14]

2.4. Data analysis

All statistical analyses were performed with SPSS (version 23, IBM, Armonk, NY, USA). Data were reported as the mean ± standard deviation or numbers (%). Statistical analysis was performed using one-way ANOVA for normally distributed data and chi-squared test or Fisher's exact tests for comparisons between frequencies. Post hoc analysis was performed if there were any significant results by ANOVA or chi-squared test. Statistical significance was accepted at $P < 0.05$.

3. Results

In total of 245 singleton infants who were admitted to the NICU were finally included; of this total number, 152 (62.0%) infants were born to women with vaginal Ureaplasma colonization, and 93 (40.0%) were born to non-colonized mothers (controls). Among 152 infants, 105 (69.0%) preterm infants were classified into the UUH group, and 47 (31.0%) were classified into the UUL group.

When the maternal factors were compared among the UUH, UUL, and control groups, the rates of preterm labor (90.5% vs. 87.2% vs. 71.0%, $P = 0.001$) and HC (66.7% vs. 48.9% vs. 43.0%, $P = 0.003$) were significantly different. Other maternal factors such as primiparity, PPROM, CC, and antenatal steroid were not different among the three groups (Table 1).

When GA was compared, the mean GA was 26.8 ± 2.3 weeks in UUH, 27.3 ± 2.3 weeks in UUL, and 27.5 ± 2.4 weeks in the control groups ($P = 0.180$) (Fig. 1A). The mean birth weight was not different among the three groups ($P = 0.165$) (Fig. 1B). Regarding stratified birth weight, very low birth weight infants (VLBWI) (i.e., <1500 g) accounted for 84.7% of UUH and 78.7% of UUL, whereas VLBWIs accounted for 81.7% of the controls ($P = 0.646$). The proportion of extremely low birth weight infants (ELBWI) below <1000 g was significantly different and was higher in UUH (55.2%), both compared to UUL (34.0%) ($P = 0.042$) and controls (35.4%) ($P = 0.015$) as in post-hoc analysis. Furthermore, post hoc analysis showed significant differences between UUH and UUL ($P = 0.042$) and between UUH and the controls ($P = 0.015$). When neonatal morbidities were compared among UUH, UUL, and the control group, the rate of RDS was not significantly different among the three groups: 88% in UUH, 72% in UUL, and 79%, respectively ($P = 0.058$). Other factors, such as PDA with treatment, sepsis, abnormal brain sonograms, and survival were also not different among the three groups (Table 2). The incidence of BPD was significantly different: 66% in UUH, 48% in UUL, and 49% in the controls ($P = 0.044$). However, when considering the severity, there was no significant difference among the three groups ($P = 0.186$) (Table 2).

Among 152 infants born to women with vaginal Ureaplasma colonization, 53 infants (34.9%) had neonatal respiratory Ureaplasma colonization, with a transmission rate of 38/105 (36.2%) in UUH and 15/47 (31.9%) in UUL ($P = 0.609$). We then further subdivided the study group according to the results of neonatal respiratory Ureaplasma colonization: infants with respiratory Ureaplasma colonization, n-UU(+) vs. noncolonized neonates, n-UU(−). In UUH, 28 of 36 n-UU (+) infants had BPD (77.8%), compared to 36 of 60 (60%) in the n-UU(−) group ($P = 0.074$). In UUL, 8 of 14 infants (57.1%) had BPD in the n-UU(+) group, compared to 12/28 (42.9%) in the n-UU(−) group ($P = 0.382$). The incidence of moderate-to-severe BPD was

Table 1 Maternal data of the study population (n = 245).

	UUH (n = 105)	UUL (n = 47)	Controls (n = 93)	*P* value
Primiparity (n) (%)	29 (28)	6 (13)	23 (25)	0.132
PPROM (n) (%)	46 (44)	20 (43)	45 (48)	0.743
Preterm labor (n) (%)	95 (91)[a]	41 (87)	66 (71)[a]	0.001
Antenatal steroid (n) (%)	93 (89)	43 (92)	84 (90)	0.841
Clinical Chorioamnionitis (n) (%)	65 (63)	23 (49)	55 (59)	0.290
Histological Chorioamnionitis (n) (%)	70 (67)[a]	23 (49)	40 (43)[a]	0.003

Abbreviations: PPROM, preterm premature rupture of membrane.
Post hoc analysis; a = $P < 0.05$ between UUH and controls.

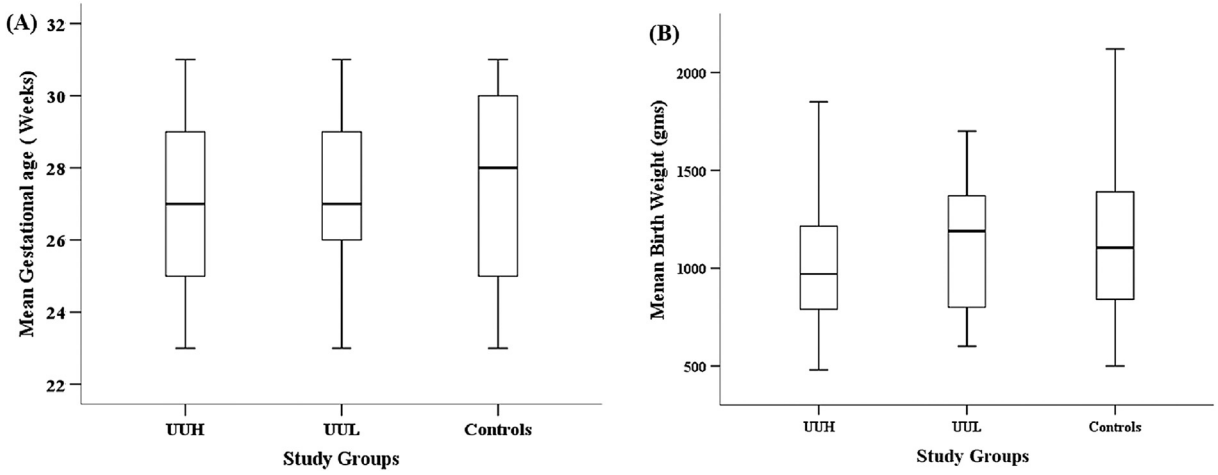

Figure 1 The mean gestational age (A) and the mean birth weight (B) of the study population did not differ significantly among the three groups. Abbreviations: UUH, high degree of maternal Ureaplasma colonization; UUL, low degree of maternal Ureaplasma colonization.

Table 2 Neonatal outcomes of the study population (n = 245).

	UUH (n = 105)	UUL (n = 47)	Controls (n = 93)	*P* value
VLBWI, <1500 g (n) (%)	89 (85)	37 (79)	76 (82)	0.646
ELBWI, <1000 g (n) (%)	58 (55)[a,b]	16 (34)[a]	33 (35)[b]	0.007
RDS (n) (%)	92 (88)	34 (72)	73 (79)	0.058
BPD (n) (%)*	63/96 (66)[c]	20/42 (48)	40/81 (49)[c]	0.044
Moderate-to-severe BPD (n) (%)*	36/96 (38)	14/42 (33)	20/81 (25)	0.186
Moderate-to-severe BPD ± death (%)	45 (43)	19 (40)	32 (34)	0.469
PDA with treatment (n) (%)*	22 (23)	8 (19)	14 (17)	0.637
Sepsis (n) (%)	12 (11)	6 (13)	10 (11)	0.827
Abnormal brain sonogram (n) (%)	17 (18)	9 (21)	13 (16)	0.519
Survival (n) (%)	96 (91)	42 (89)	81 (87)	0.614

Abbreviations: VLBW, very low birth weight infants; ELBWI, extremely low birth weight infants; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus.
*Those who died before diagnosis were excluded from the statistical analysis.
Post hoc analysis: a = $P < 0.05$ between UUH and UUL; b = $P < 0.05$ between UUH and controls; c = $P < 0.1$ between UUH and controls.

38.8% (14/36) in the n-UU(+) of UUH and 42.9% (6/14) in n-UU(+) of UUL ($P = 0.041$) (Table 3).

4. Discussion

In this study, we confirmed that maternal vaginal Ureaplasma colonization was associated with preterm labor and HC leading to preterm delivery, as documented in recent reports.[6,15] Additionally, these values tended to increase as the density of maternal Ureaplasma increased; in other words, high-degree maternal Ureaplasma colonization was associated with higher incidences of preterm labor and HC, compared to the noncolonized group. Notably, we observed more frequent development of BPD in the maternal high-degree colonized group together with

Table 3 Incidence of Bronchopulmonary Dysplasia in the Maternal Ureaplasma colonized Group.

	UUH(n = 105)		UUL (n = 47)		*P* value
	n-UU(+) (n = 38)	n-UU(−) (n = 67)	n-UU(+) (n = 15)	n-UU(−) (n = 32)	
BPD (n) (%)*	28/36 (78)[a]	36/60 (60)	8/14 (57)	12/28 (43)[a]	0.041
Moderate-to-severe BPD (n) (%)*	14/36 (39)	22/60 (37)	6/14 (43)	8/28 (29)	0.779

*Those who died before diagnosis were excluded from the statistical analysis.
Post hoc analysis; a = $P < 0.05$ between UUH + n-UU(+) and UUL + nUU(−).

neonatal respiratory Ureaplasma colonization group than in the low-degree colonized with noncolonized premature infants born less than 32 weeks of GA.

Although numerous studies have been conducted to determine the association between Ureaplasma colonization and BPD, controversies remain. Most of the earlier studies found that Ureaplasma colonization was associated with preterm delivery with no significant association between Ureaplasma colonization and BPD after correction for GA.[16–18] In these studies, BPD was defined as a persisting oxygen requirement at 28 days after birth, and severity was not evaluated. However, most neonatologists are now interested in BPD at 36 weeks of PMA as a chronic lung disease with severity classification rather than BPD at 28 days of life, as defined only by oxygen dependency. Thus, studies addressing Ureaplasma according to the severity of BPD might be more important.

A recent meta-analysis reported that neonatal pulmonary Ureaplasma colonization was significantly associated with the development of BPD, both at 36 weeks' PMA and at 28 days of life, although BPD at 28 days of life might instead reflect lung immaturity.[19] Van Waarde et al.[16] reported that Ureaplasma was associated with GA and/or low birth weight, but not BPD, in mechanically-ventilated infants. Some reports have described a significant association between Ureaplasma colonization and BPD; however, these results disappeared following multivariate analysis, including correction for gestational age.[18,20] In our study, the incidence of BPD at 36 weeks of GA was higher in infants born to women with Ureaplasma colonization, and in the high-density maternal colonized group compared to the noncolonized group. However, there was no difference in the incidence of BPD between the maternal high-degree and low-degree colonized groups.

Since most neonatologists are interested in BPD at 36 weeks' PMA, rather than BPD at 28 days of life, as defined only by oxygen dependency, studies of Ureaplasma according to the severity of BPD might be more important. Hence, the severity of BPD was compared among the three groups in our study. In this study, the presence of moderate-to-severe BPD was not different among the groups of infants born to women with high-degree or low-degree Ureaplasma colonization and the noncolonized group. These findings might explain why the causal relationship between Ureaplasma colonization and BPD remains unclear and suggest that postnatal factors are also important for the development of BPD.

To investigate the perinatal transmission rate from mother to neonate, we analyzed the presence of Ureaplasma in infants' respiratory tract samples. The vertical transmission rate during pregnancy is 18%–55% for full term infants and 22%–58% for preterm infants.[8,20] The vertical transmission rate for ELBWI is as high as 89%.[21] In our study, the rate of neonatal respiratory Ureaplasma colonization, i.e., the vertical transmission rate, was 35% in preterm infants born before 32 weeks of GA with no difference between UUH (36%) and UUL (32%), similar to the results of other studies. To further investigate the effect of vertical transmission on the development of BPD, we subdivided the study group according to the results of neonatal respiratory Ureaplasma colonization, i.e., n-UU(+) and n-UU(−), and then analyzed the incidence of BPD. In our study, the development of BPD was greater among respiratory Ureaplasma colonized infants born to women with high-degree colonization than noncolonized infants born to women with low-degree colonization ($P < 0.05$). However, the incidence of moderate-to-severe BPD was not different. Hence, neonatal respiratory colonization might have some effect on the higher rate of BPD, in association with high-degree maternal colonization.

With respect to maternal factors, recent studies have indicated a strong relationship between maternal Ureaplasma colonization and pregnancy outcomes.[22,23] Kallapur et al.[24] found that an ascending infection through the cervix to the choriodecidual space led to generalized inflammation and produced proinflammatory mediators that initiated preterm labor. The mechanism by which Ureaplasma colonization of the lower genital tract causes intrauterine infection and finally leads to adverse pregnancy outcomes remains unclear. However, a recent study suggested that extracellular collagen fragmentation with protease induced by Ureaplasma caused preterm rupture of the membranes and that neutrophil influx by Ureaplasma contributed to the development of chorioamnionitis.[25] Other studies have reported that Ureaplasma was frequently isolated when chorioamnionitis is present, and that 80% of women who deliver at <30 weeks' gestation have HC.[26,27] In our study, although the frequency of CC was not significantly different between Ureaplasma-colonized and noncolonized mothers, the frequency of HC was higher in Ureaplasma colonized mothers than in the controls, similar to the results of other reports. In addition, in this study, maternal high-density Ureaplasma-colonization was associated with a higher incidence of preterm labor and HC compared to the controls, as reported in a previous study.[12]

Our study has several limitations. First, because the study was performed retrospectively, we could not control for the effects of maternal antibiotic use, including the use of macrolides, on clinical outcomes. Second, although there might be some differences in the pathology of BPD according to Ureaplasma serovar, such as *Ureaplasma urealyticum* and *Ureaplasma parvum*, we could not observe these differences because the kit that we used in the study period could not distinguish the two. However, the strength of our study is that we attempted to demonstrate the relationship between the degree of maternal Ureaplasma colonization and vertical transmission, i.e., neonatal respiratory Ureaplasma colonization, and to identify the relationship between BPD and Ureaplasma. To the best of our knowledge, this study is the first to demonstrate such relationships.

In conclusion, we demonstrated that maternal Ureaplasma colonization was related to the development of BPD, and that maternal high-density vaginal colonization was associated with an increased risk for BPD in preterm infants of <32 weeks of GA. With high-degree Ureaplasma colonization and neonatal respiratory colonization, the increase in the incidence of BPD was even greater. Hence, selective and special care is needed for very preterm infants of <32 weeks' GA with maternal vaginal Ureaplasma colonization. Further well-designed prospective cohort studies are also warranted to confirm the association between Ureaplasma colonization and the presence of BPD.

Conflict of interest

No conflicts of interest are declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2018.11.004.