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The prevalence of abnormal vaginal flora and predictive factors for intrauterine infection in pregnant Korean women with preterm labor

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Summary

Objective: To investigate the prevalence of abnormal vaginal flora (AVF) and predictive factors for intrauterine infection in pregnant Korean women with preterm labor. *Materials and Methods:* The authors reviewed the medical records of 106 pregnant Korean women with preterm labor admitted to Eulji Medical Center between January 2006 and August 2011. The results of vaginal discharge tests and maternal serum C-reactive protein (CRP) level at admission, placental biopsy, and perinatal outcomes were searched. The prevalence of abnormal vaginal flora was calculated. The perinatal outcomes and predictive factors for intrauterine infections were analyzed based on placental pathology and early-onset neonatal sepsis. *Results:* The prevalence of abnormal vaginal flora was 75.4%. *Ureaplasma urealyticum (UU)*, intermediate flora, Candidiasis, bacterial vaginosis, and aerobic bacterial colonization were detected in 40.6%, 38.7%, 17%, 14.2%, and 11.3% of the women, respectively. The frequency of early-onset neonatal sepsis was significantly different between women with aerobic bacterial colonization and those with normal flora ($p = 0.008$). An elevated maternal serum CRP level was an independent intrauterine infection predictor (odds ratio, 1.918; 95% confidence interval, 1.102−3.338; $p = 0.048$). *Conclusion:* Aerobic bacterial colonization may predict early-onset neonatal sepsis. An elevated maternal serum CRP level was an independent intrauterine infection predictor based on placental infections and early-onset neonatal sepsis.

Key words: Maternal serum C-reactive protein level; Spontaneous preterm labor; Pregnancy; Microorganisms; Predictor.

Introduction

Intrauterine infection (IUI) is observed in 30–50% cases of preterm birth [1]. The main causative mechanism of IUI may be an ascending infection from a vaginal infection. IUI is associated with abnormal vaginal flora (AVF) that cause bacterial vaginosis (BV) and aerobic vaginitis (AV), as well as *Ureaplasma urealyticum (UU)* infection, and *Mycoplasma hominis (MH)* infection [2-10].

Ascending infection from vaginal infections progresses to choriodecidual infections, intra-amniotic infection (IAIs), and fetal infections. To date, IUI have been diagnosed in the amniotic fluid of women with preterm labor by using markers; for detecting IUI, the levels of cytokines such as interleukin-6 and -8 determine the presence of some microorganisms such as *UU* in the amniotic fluid [11-12]. However, amniocentesis may cause anxiety in some patients and obstetricians because of adverse risks, such as preterm labor, preterm birth, and IUI [13]. Although there is sufficient evidence for the use of infectious markers in amniotic fluid as diagnostic tools for IUI, their use in clinical practice is limited [11-13]. Therefore, a non-invasive diagnostic tool is very important for the diagnosis of IUI in women with preterm labor.

The C-reactive protein (CRP) level in the maternal serum is a predictor of preterm labor [14-20]. Moreover, the CRP level in the maternal serum might be an indicator of IAIs [19]. In addition, maternal serum CRP levels can be used as a predictor of funisitis and early-onset neonatal sepsis (ENS) [20]. Without any other apparent infection foci, maternal serum CRP levels or AVF prevalence at admission may be increased in women with IUI.

The present authors hypothesized that the prevalence of AVF and the level of CRP in maternal serum at admission will be more elevated in women with IUI, classified as the presence of placental and fetal infections, because they could not perform amniocentesis. For verifying the hypothesis, they reviewed the medical records for results of AVF and the level of CRP in maternal serum at admission, and perinatal outcomes. The presence of placental infections was defined as either chorioamnionitis, funisitis, or intervillositis based on placental biopsy after delivery [21]. Fetal infections were defined as ENS.

The authors aimed to evaluate the prevalence of AVF at admission in pregnant Korean women with preterm labor and predictive factors for IUI based on placental and fetal infections.

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Materials and Methods

The medical records of pregnant women with spontaneous preterm labor at 24-36 weeks' gestation who were admitted to the Eulji University Hospital in Daejeon between January 2006 and August 2011 were reviewed. Patients with clinical chorioamnionitis that needed immediate delivery, and patients with other infectious or inflammatory diseases were excluded from the study. A total of 224 pregnant women were found. Of this group, 118 women were excluded, because they had other causes of preterm birth or medical diseases such as preeclampsia (n=4), uterine anomaly (n=3), uterine myoma (n=7), placenta previa (n=1), twin pregnancy (n=87), gestational diabetes mellitus (n=10), and other inflammatory diseases (n=6). A total of 106 women were finally included after obtaining written informed consent. Among 106 patients, four women had a term delivery, and the others had a preterm delivery. This study was approved by the Institutional Review Board (IRB no.: 2014-10-002).

The results of Gram staining to compute Nugent scores for intermediate flora and bacterial vaginosis, wet mount for candidiasis, culture for *MH* and *UU*, and conventional culture were reviewed retrospectively [22-24]. In addition, the CRP level was noted at admission. After delivery, white blood cell counts and CRP levels of neonates within 24 hours after birth were found. The result of placental pathology was also reviewed. Normal flora was classified as the result of vaginal samples without AVF. This group was used as control for comparison to the group with AVF

The serum CRP levels were measured with a latex-enhanced turbidimetric immunoassay using an automated analyzer. The measurement range of this assay is 0.3–300 mg/L. This result was changed to the logarithmic value for normal distribution.

Placental pathology

The results of placental pathology were reviewed. Chorioamnionitis was defined as the migration of maternal neutrophils from the membranous chorionic trophoblast to the amnion. Intervillositis indicated infiltration of maternal neutrophils in the intervillous space, and funisitis occurred at a later stage in which fetal neutrophils migrated from the umbilical arteries into Wharton's jelly. The presence of placental infections was defined as either chorioamnionitis, funisitis, or intervillositis based on the results of placental biopsy after delivery [21].

Perinatal outcomes - general

The gestational age at birth, birth weight, and Apgar scores at one and five minutes were reviewed in all the patients. ENS was defined as proven positive blood culture and suspected negative blood culture, along with more than three of the following categories of positive clinical signs within three days of birth: (1) unstable body temperature for > one hour (axillary temperature: fever > 37.5°C, hypothermia < 36.5°C), (2) cardiovascular abnormality (heart rate < 100 or > 160 per minute, hypotension requiring inotropic agents), (3) respiratory abnormality (respiration rate > 60 per minute, dyspnea, apnea, increased oxygen demand or treatment with mechanical ventilator), (4) metabolic acidosis (arterial blood gas analysis: pH < 7.35, base deficit ≥ 6), (5) gastrointestinal tract abnormality (vomiting, abdominal distension, abnormal gastric intolerance, bloody stool, and umbilical erythema), (6) neurological abnormality (drowsiness, muscle weakness, excessive irritability, and convulsions).

Intrauterine infections

The authors used the placental pathology and the presence of ENS after delivery as diagnostic tools for IUI. The IUI group included women with placental infections or those with ENS. The women with normal placental pathology and women whose neonates did not have infectious sign were classified as the control group. Perinatal outcomes were compared between the IUI and the control groups. The authors analyzed the prevalence of AVF as predictive factors of IUI.

Table 1. — *The prevalence of abnormal vaginal flora in pregnant Korean women with spontaneous preterm labor (n = 106).*

	Frequency	Percentage
Abnormal vaginal flora	80	75.4
Intermediate flora	41	38.7
Bacterial vaginosis	15	14.2
Aerobic bacterial colonization	12	11.3
Ureaplasma urealyticum infection	43	40.6
Mycoplasma hominis infection	1	0.9
Candidiasis	18	17.0
Normal flora	26	24.5

Statistical analysis

SPSS ver. 18.0 was used for the statistical analysis of the study results. Statistical significance was determined using the Pearson chi-square test. The mean values were analyzed using the Mann-Whitney test owing to a non-normal distribution. A probability value of < 0.05 was considered statistically significant. The logarithmic value of the serum CRP level was used for the analysis because of the non-normal distribution of the actual numeric values. A multiple logistic regression model was used to determine the predictive factors of IUI.

Results

A total of 106 women with spontaneous preterm labor were included in this study. The mean age was 31 years, mean parity was 0.75, mean gestational age at birth was 33.7 weeks, and mean birth weight was 2.24 kg. Table 1 shows the prevalence of AVF. *UU* infection showed the highest prevalence. The prevalence of Candidiasis was 18.0% (18/106) considering the results of wet mounts. On aerobic culture, 24 women had positive results: candidiasis in 12 women, *Enterococcus faecium* in five, *Escherichia coli* in three, and *Staphylococcus aureus*, *Pseudomonas aeruginosa*, group B streptococcus, and *Klebsiella pneumoniae* in one patient each. Among these, the patients with positive *Candida albicans* culture were excluded from the study, because the diagnosis of candidiasis was made on the basis of a wet mount. Twelve women were classified as having aerobic bacterial colonization (ABC). In total, 26 women with normal flora were classified as the control group.

ENS was reported in 12 women. Only one neonate had positive blood cultures. Other cases were diagnosed based on clinical findings. The present authors could only obtain the results of placental pathology in 93 women: 38 had normal findings, 18 had placental infections, and 37 had other findings. Among placental infections, 17 were chorioamnionitis with or without intervillositis and funisitis, and one

Table 2. — *Perinatal outcomes according to abnormal vaginal flora in pregnant Korean women with spontaneous preterm labor.*

Characteristics	Intermediate flora n=41	Bacterial vaginosis n=15	Aerobic bacterial colonization n= 12	*Ureaplasma urealyticum* n=43	Candidiasis n= 18	Normal flora (control) n=26
GA at birth (weeks)	33.1 (3.5)	33.5 (3.7)	32.7 (4.0)	33.6 (3.3)	33.1 (3.5)	34.4 (3.1)
Birth weight (grams)	2145 (759)	2190 (747)	2053 (794)	2231 (710)	2132 (704)	2441 (704)
Apgar score at 1 minute	5.2 (2.1)	5.9 (2.7)	5.8 (2.1)	5.3 (2.2)	5.1 (1.7)	5.0 (2.2)
Apgar score at 5 minutes	7.7 (1.6)	7.8 (1.7)	7.9 (1.1)	7.8 (1.5)	7.5 (1.5)	7.3 (1.5)
Placental infection (n)	7	3	2	8	4	6
Neonatal sepsis (n)	4	2	4*	3	5	3
Neonatal WBC (/ml)	14573 (9668)	11715 (4368)	10372 (4776)	13672 (9021)	14603 (5856)	11281 (4796)
Neonatal CRP (mg/L)	1.0 (2.2)	0.6 (0.5)	0.9 (0.7)	0.8 (0.9)	1.8 (3.3)	1.4 (1.7)
Maternal CRP (mg/L)	8.4 (16.2)	22.1 (33.3)	21.5 (38.2)	10.2 (18.6)	7.8 (11.2)	9.2 (14.0)

GA, gestational age; WBC, white blood cell; CRP, C-reactive protein; SD, standard deviation. Data are presented as the mean (SD). Gestational age at birth, birth weight, Apgar score, neonatal WBC, and neonatal CRP were analyzed by using the Mann-Whitney test owing to non-normal distribution.
The test for normality was performed by using the Shapiro-Wilk test. Placental infection and neonatal sepsis were analyzed with χ^2 test. * $p < 0.05$.

Table 3. — *The perinatal outcomes of intrauterine infection in pregnant women with spontaneous preterm labor.*

	IUI (n=24)	Control (n=31)	*p* value
Age (years)	30.7±4.0	31±4.9	0.794
Parity	0.8±0.9	0.7±0.9	0.821
Gestational age at birth (weeks)	31.5±4.9	34.1±2.5	0.357
Birth weight (grams)	1911±1033	2222±583	0.141
Apgar score 1 minute	4.3±2.4	5.3±2.2	0.09
Apgar score 5 minutes	7.1±1.5	7.6±1.4	0.145
Neonatal WBC	16604±12021	11315±3554	0.191
Log CRP level (mg/L)	2.07±1.46	1.09±0.92	0.007*

Data are given as mean (SD). SD, standard deviation;
IUI, intrauterine infection; WBC, white blood cell; CRP, C-reactive protein.
Data were analyzed by using the Mann-Whitney test owing to non-normal distribution. The test for normality was performed by using the Shapiro-Wilk test.
* *p* value < 0.05.

was intervillositis without chorioamnionitis. Six of these women had both placental infections and ENS. Therefore the IUI group included 24 women with placental infection or ENS, while the control group included 36 women with normal placental finding and no fetal infection.

The present authors compared the perinatal outcomes between the pregnant women with AVF and those with normal flora (Table 2). There were no significant differences in perinatal outcomes or placental infections in pregnant women with BV, intermediate flora, *UU* infection, or candidiasis ($p > 0.05$ for all) compared to those with normal flora, respectively. The mean gestational age at birth was not significantly different between patients with BV, ABC, or *UU* infection and those with normal flora. However, there was a significant difference in the frequency of ENS between patients with ABC, and those with normal flora ($p = 0.008$, Table 2). The authors could not analyze the perinatal outcomes of patients with MH infection because there was only one case.

Table 3 shows the perinatal outcomes of the IUI and the control groups. There was no statistical significance for GA at birth, Apgar scores, and birth weight. However, log maternal serum CRL level at admission showed a statistically significant difference between the two groups.

To determine the clinical value in the prediction of IUI, the authors conducted multiple logistic regression analysis with the presence of BV, ABC, *UU* infection, and maternal serum CRP level (Table 4). An elevated maternal serum CRP concentration was a better independent predictor of IUI (odds ratio, 1.918; 95% confidence interval, 1.102−3.338) compared to BV, AV, and UU infection.

Table 4. — *Multiple logistic regression analysis for predicting intrauterine infection.*

	β	S. E.	*P* value	OR	95% CI	
					Lower	Upper
Bacterial vaginosis	0.151	1.143	0.895	1.163	0.124	10.931
Aerobic bacterial colonization	0.463	0.895	0.605	1.588	0.275	9.176
Ureaplasma urealyticum	0.616	0.649	0.342	1.852	0.519	6.607
Maternal serum CRP level	0.651	0.283	0.021	1.918	1.102	3.338

S. E., standard error of β coefficient; OR, odds ratio; CI, confidence interval; CRP, C-reactive protein.

Discussion

In the present study, the prevalence of AVF was 75.4%. *UU* infection intermediate flora, candidiasis, bacterial vaginosis, and aerobic bacterial colonization were detected, in order of prevalence, in the pregnant Korean women with spontaneous preterm labor. The presence of AVF was not associated with placental infections. However, ABC was associated with ENS. The maternal serum CRP level may be a better independent predictive factor than AVF for IUI based on placental infections and ENS.

This study is important because the authors showed the prevalence of AVF and its clinical significance in pregnant Korean women with preterm labor. In particular, they showed that the maternal serum CRP level at admission may be a predictive factor for IUI; this may be important for determining the strategy of management in pregnant women with preterm labor.

Among AVF, *UU* had the highest prevalence in this study. *UU* infection was reported to be associated with preterm labor [9-10]. As culturing *UU* is very difficult, the biological characteristics and IUI mechanism of this microorganism have not been well-documented. Although *UU* colonization within the vagina is associated with preterm birth, not all cases may be pathogenic because these microorganisms can exist as normal flora in the vagina. In the present study, the authors found no association between exposure to *UU* and adverse pregnancy outcomes. Some researchers have asserted that *MH* and *UU* may be the causative microorganisms of preterm birth [9-10]. Donders *et al.* showed that women carrying *MH* commonly experienced preterm labor [9]. In addition, *Mycoplasmata* are potentially pathogenic microorganisms, resulting in an increased risk in PROM, chorioamnionitis, and neonatal infections [24]. Unfortunately, owing to few reported cases, it was not possible to evaluate the risk of *MH* on pregnancy in the present study.

BV is one of the most common vaginal infections that induce preterm labor. BV cannot induce inflammation but can deform immunoglobulin A, a process that may incapacitate the vaginal defense mechanism. Therefore, the role of BV has been thought to enable other microorganisms within the vagina to ascend to the uterus [25-27]. While BV occurs typically without any host vaginal immune response, AV causes real vaginitis. Aerobic enteric commensals consist of *E. coli*, *S. aureus*, group B streptococcus, *Klebsiella* species, and *Enterococci* [7-8]. These microorganisms can induce inflammatory responses in the female genital tract; these responses are potentially important factors in the pathogenesis of preterm labor [7-8]. Donders *et al.* stated that AV consisted of absent lactobacillary flora and predominant aerobic microflora in the vagina using the AV scoring system [28]. However, the present authors used conventional culture for the diagnosis of AV instead of the AV score, considering that conventional culture is one of the most commonly used methods to diagnose vaginitis and lower genital tract infections. However, the detection rate for determining the causative bacteria for vaginitis is low, owing to different optimal culture conditions. Nevertheless, bacterial culture is important for the diagnosis of organisms causing infectious disease, which helps in treating such patients; antibiotic susceptibility tests are very helpful to determine the optimal antibiotics that should be administered to patients. In the present study, some microorganisms were isolated. Although the present data did not show a significant correlation between ABC and placental infections, it proved that ABC influenced ENS.

AV, both detected clinically and confirmed by culture, was related to an increased risk of chorioamnionitis and funisitis, and neonatal sepsis is caused by AV rather than BV, mainly group B streptococcus, *E. coli,* and *S. aureus* [29]. Moreover, aerobic abnormal flora, mixed flora, and organisms causing partial BV (intermediate flora) were associated with preterm birth, especially at < 34 weeks' gestation, and pregnant women with intermediate flora tended to progress to preterm labor [7]. Intermediate flora includes anaerobic and aerobic flora as well as few lactobacilli. Such flora can ascend easily into the intrauterine cavity. Donders *et al.* studied the role of AV and BV in preterm labor and found that partial BV and AV could more easily induce preterm labor compared to complete BV [28]. Unlike the other reports, the result did not show differences in perinatal outcomes. Those results may be associated with the sampling time. Sampling in their study was conducted within gestation 20 weeks without preterm labor. In the present study, the sampling was conducted at admission because of spontaneous preterm labor. Therefore, time discrepancy may have influenced the results. However, ABC at admission could predict ENS. Furthermore, the maternal serum CPR level may predict IUI based on placental pathology and fetal infections in patients with preterm labor. Therefore, the present authors recommend that the text for AVF be performed within gestation 20 weeks for prediction of IUI. After onset of preterm labor, maternal serum CRP level may be useful for prediction of IUI. Moreover, AVF test after onset of preterm labor will give the information ENS and perinatal infection in neonates.

This study has some limitations. (1) In the IUI cases, IAI cases with normal placenta and neonates without ENS were excluded because the authors could not perform amniocentesis. There may have been some bias despite the few cases. (2) The number of patients included in this study was small. Hence, further studies with larger number of patients are needed to elucidate the influence of IAIs on the perinatal outcomes. Therefore, AVF and maternal serum CPR levels help predict and manage IUI in pregnant women with preterm labor.

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