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# Effect of Prenatal Antibiotic Exposure on Neonatal Outcomes of Preterm Infants

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## ABSTRACT

**Purpose:** Antibiotic exposure during pregnancy may affect the fetus and newborn in many ways. This study investigated the impact of prenatal antibiotic exposure duration on neonatal outcomes in very preterm (VP) or very low birth weight (VLBW) infants.
**Methods:** From September 2015 to December 2020, preterm infants with gestational age less than 32 weeks or with a BW less than 1,500 g who were admitted to the neonatal intensive care unit, and their mothers were enrolled. Prenatal antibiotic exposure was defined as antibiotics received by mothers before delivery, and the patients were categorized into the non-antibiotic group, short-duration (SD; ≤7 days) group, or long-duration (LD; >7 days) groups.
**Results:** A total of 93 of 145 infants were exposed to prenatal antibiotics, among which 35 (37.6%) were in the SD group and 58 (62.4%) were in the LD group. Infants in the LD group had a significantly higher birth weight-for-gestational-age (BW/GA) Z-score than those in the non-antibiotic group, even after the adjustment for confounding factors (beta, 0.258; standard error, 0.149; $P$<0.001). Multivariate logistic regression analysis showed that prolonged prenatal antibiotic exposure was independently associated with death (adjusted odds ratio [aOR], 8.926; 95% confidence interval [CI], 1.482–53.775) and composite outcomes of death, necrotizing enterocolitis (NEC), and late-onset sepsis (LOS) (aOR, 2.375; 95% CI, 1.027–5.492).
**Conclusions:** Prolonged prenatal antibiotic exposure could increase the BW/GA Z-score and the risk of death and composite outcomes of death, NEC, and LOS in VP or VLBW infants.

**Keywords:** Anti-bacterial agents; Infant, premature; Maternal exposure

## INTRODUCTION

Antibiotics are widely prescribed to women during pregnancy, most commonly during the perinatal period. Some reports noted that antibiotics account for nearly 80% of all prescription medications during pregnancy and that approximately 25–40% of women will receive at least one antibiotic during pregnancy.[1,2] Although antibiotics are necessary for treating infections during pregnancy, such as bacterial vaginosis, urinary tract infections, and upper respiratory tract infections, they are often prescribed to prevent infections.[1,3] In particular, maternal group B streptococcus (GBS) colonization and preterm prelabor rupture of the membranes (PPROM) are absolute indications for prophylactic intrapartum antibiotic administration.[4,5]

Several studies have reported a correlation between prenatal antibiotic exposure and neonatal outcomes. Bizzarro et al.[6] reported that the increasing use of intrapartum antibiotics was associated with increased ampicillin-resistant *Escherichia coli* early-onset sepsis and *E. coli* late-onset sepsis (LOS) in preterm and full-term infants. Likewise, Didier et al.[7] demonstrated that maternal antibiotic exposure was associated with the risk of amoxicillin-resistant *E. coli* infections. Weintraub et al.[8] reported that prenatal exposure to ampicillin was associated with an increased risk of necrotizing enterocolitis (NEC). However, some studies focused on the protective effect of prenatal antibiotics. Mercer et al.[9] also found that prenatal antibiotic exposure in mothers with PPROM could reduce the incidence of combined neonatal outcomes, respiratory distress, and NEC. Reed et al.[10] also suggested that prenatal antibiotic exposure was associated with lower rates of NEC and mortality among very preterm (VP) infants. As such, neonatal outcomes associated with prenatal antibiotic exposure have been reported inconsistently among studies. Moreover, few studies have examined neonatal outcomes of preterm infants according to prenatal antibiotic exposure duration.

This study aimed to investigate the effects of maternal antibiotic exposure duration on neonatal outcomes of VP or very low birth weight (VLBW) infants.

## MATERIALS AND METHODS

### 1. Study design and population

We conducted a retrospective cohort study of infants who were admitted to the neonatal intensive care unit of a South Korean tertiary hospital between September 2015 and December 2020 with a gestational age (GA) of <32 weeks or birth weight (BW) <1,500 g.

Maternal antibiotic exposure was defined as antibiotic treatment prior to delivery. Indications for maternal antibiotic exposure included: 1) PPROM; 2) clinical chorioamnionitis; 3) GBS prophylaxis; 4) C-reactive protein elevation; 5) other infections such as urinary tract infections; bacterial vaginitis, and respiratory infections; and 6) prophylaxis after procedures such as amnioinfusion, amnioreduction, or the McDonald operation. We excluded cases of antibiotics administered for delivery. PPROM is among the most common indications for maternal antibiotic exposure, and the administration of broad-spectrum antibiotics reduces infection and neonatal morbidity. The American College of Obstetricians and Gynecologists (ACOG) recommended 7-day therapy of latency antibiotics during the management of mothers with PPROM.[5] Therefore, we divided the patients according to prenatal antibiotic exposure duration into the non-antibiotic, short-duration (SD; ≤7 days), or long-duration (LD; >7 days) groups.

### 2. Ethics statement

The study protocol was approved by the Institutional Review Board of Korea University Anam Hospital (No. 2020AN0540), which waived the need for informed consent. Patient records and information were anonymized and identified prior to the data analysis.

### 3. Clinical data collection

Data were collected from the maternal and neonatal hospital records. Clinical characteristics including maternal age, delivery type, GA at birth, single vs. multiple birth status, in vitro fertilization, PPROM, histological chorioamnionitis, gestational diabetes mellitus (GDM), and pregnancy-induced hypertension (PIH) were documented. GDM was defined as a variable


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degree of glucose intolerance with onset or first recognition during pregnancy. PIH referred to hypertension with onset in the latter part of pregnancy (>20 weeks' gestation), followed by normalization of the blood pressure postpartum. The infants' weights, lengths, and head circumferences at birth and discharge were collected. The Z-scores of weight, length, and head circumference-for-GA were calculated using the Fenton growth chart.[11] Small for GA and large for GA were defined as a BW below the 10th percentile and above the 90th percentile according to this growth chart, respectively. Postnatal mortality and morbidities including NEC, LOS, moderate-to-severe bronchopulmonary dysplasia (msBPD), and severe neurologic injury such as intraventricular hemorrhage ≥ grade III or periventricular leukomalacia or retinopathy of prematurity (ROP) were also reviewed. NEC was staged using modified Bell's staging criteria,[12] while msBPD was defined as the need for supplemental oxygen or positive pressure at 36 weeks postmenstrual age according to the National Institute of Child Health and Human Development definition.[13] LOS was defined as blood culture–positive sepsis accompanied by systemic antibiotic treatment for more than 5 days occurring after 72 hours of age.[14] ROP was staged according to the International Classification of Retinopathy of Prematurity, Third Edition.[15]

### 4. Statistical analysis

The statistical analysis was performed using SPSS (version 23.0; IBM Co., Armonk, NY, USA). The patients' baseline characteristics are displayed as frequencies and percentages or summarized as the median and interquartile range. Differences between continuous variables were assessed using the Kruskal-Wallis or Mann-Whitney U test. Differences between categorical variables were analyzed using the $\chi^2$ or Fisher's exact test. A multiple linear regression analysis was conducted to adjust for confounders in the BW-for-gestational-age (BW/GA) Z-score. Multivariate logistic regression analysis was used to estimate the risk of neonatal morbidities and mortality based on prenatal antibiotic exposure duration. Statistical significance was defined as $P<0.05$.

## RESULTS

During the study period, 145 infants were enrolled in the study. Of them, a total of 93 (64%) were exposed to prenatal antibiotics: 35 (37.6%) in the SD group and 58 (62.4%) in the LD group (**Fig. 1**).

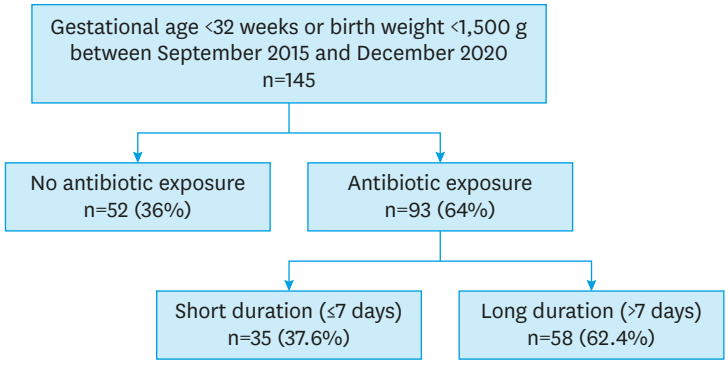


**Fig. 1.** Flow diagram of the study population.


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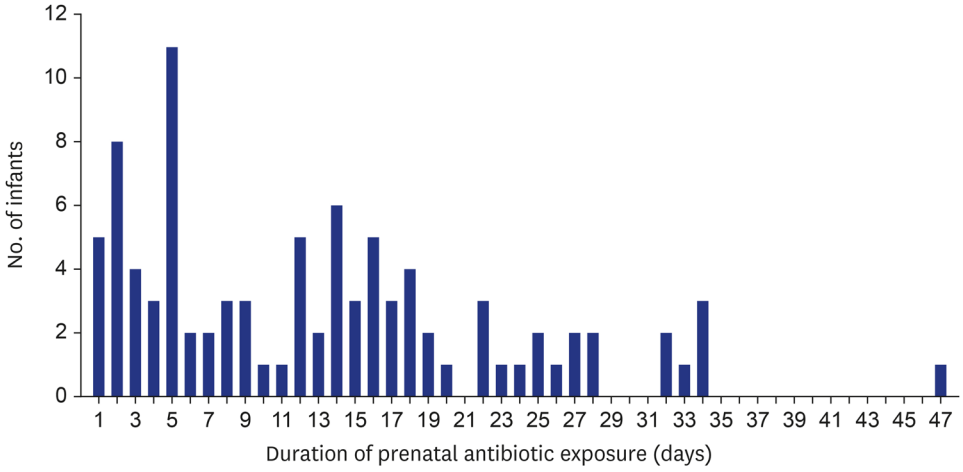


**Fig. 2.** Distribution of infants according to prenatal antibiotic exposure duration.

## 1. Characteristics of prenatal antibiotic exposure

**Fig. 2** shows the distribution of infants according to prenatal antibiotic exposure duration. The median durations were 4 days and 17 days in the SD and LD groups, respectively (**Table 1**). Seven (11.6%) infants in the LD group were exposed to prenatal antibiotics for more than 1 month. PPROM was the most common indication for prenatal antibiotic exposure (54.3% in the SD group, 58.6% in the LD group). Most infants were exposed to 3 or more prenatal antibiotics, but there were no significant differences in the number of exposed antibiotics between the SD and LD groups. The most common combination of antibiotics was cephalosporins, metronidazole, and clarithromycin. Cephalosporins was the most commonly prescribed antibiotic in both groups (91.4% in the SD group, 93.1% in the LD group). Clarithromycin and ampicillin/sulbactam were prescribed more frequently in the LD group than in the SD group.

**Table 1.** Characteristics of prenatal antibiotic exposure

| Characteristics of prenatal antibiotic exposure | Antibiotic exposure | | *P* |
|---|---|---|---|
| | SD (n=35) | LD (n=58) | |
| Duration of maternal antibiotic exposure (days) | 4 (2–5) | 17 (13–24) | <0.001 |
| Indications of maternal antibiotic exposure | | | |
| PPROM | 19 (54.3) | 34 (58.6) | 0.682 |
| CRP elevation | 1 (2.9) | 3 (5.2) | >0.990 |
| Pneumonia | 1 (2.9) | 0 (0) | 0.376 |
| Preterm labor | 6 (17.1) | 2 (3.4) | 0.049 |
| Post-amnioinfusion or amnioreduction | 3 (8.6) | 6 (10.3) | >0.990 |
| Post-McDonald operation | 0 (0) | 10 (17.2) | 0.012 |
| Other | 5 (14.3) | 3 (5.2) | 0.148 |
| No. of exposed antibiotics | | | 0.129 |
| 0 | 0 (0) | 0 (0) | |
| 1 | 4 (11.4) | 1 (1.7) | |
| 2 | 2 (5.7) | 3 (5.2) | |
| ≥3 | 29 (82.9) | 54 (93.1) | |
| Type of antibiotics | | | |
| Cephalosporins | 32 (91.4) | 54 (93.1) | 1.000 |
| Metronidazole | 28 (80.0) | 53 (91.4) | 0.113 |
| Clarithromycin | 24 (68.6) | 52 (89.7) | 0.011 |
| Ampicillin/Sulbactam | 7 (20.0) | 52 (89.7) | <0.001 |
| Others | 6 (17.1) | 7 (12.1) | 0.494 |

Values are presented as median (interquartile range) or number (%).
Abbreviations: CRP, C-reactive protein; LD, long-duration (>7 days); PPROM, preterm prelabor rupture of the membranes; SD, short-duration (≤7 days).


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## 2. Maternal and infant characteristics according to prenatal antibiotic exposure duration

Maternal age, PPROM duration, frequency of cesarean delivery, multiple pregnancies, histologic chorioamnionitis, GDM, and PIH were statistically different among the 3 groups (**Table 2**). PPROM duration was longest in the LD group (median: 0, 7, and 24 hours in the non-antibiotic, SD, and LD groups, respectively; $P<0.001$). Histologic chorioamnionitis and GDM were significantly more frequent in the LD group, whereas PIH was most frequent in the non-antibiotic group. There were no significant differences in maternal characteristics other than frequency of cesarean delivery, PPROM duration, and GDM between the SD and LD groups. There was no significant difference in antenatal corticosteroid use among the 3 groups.

The GA differed significantly among the 3 groups (mean: $30^{+5}$, $30^{+1}$, and $28^{+0}$ weeks in the non-antibiotic, SD, and LD groups, respectively; $P<0.001$) (**Table 2**). The LD group had the highest rate of extremely preterm infants (13.5%, 17.1%, and 48.3% in the non-antibiotic, SD, and LD groups, respectively; $P<0.001$). The LD group had a significantly higher mean BW/GA Z-score than the non-antibiotic group, which persisted even after the adjustment for a GA less than 28 weeks, cesarean delivery, maternal age, multiple pregnancy, histologic chorioamnionitis,

**Table 2.** Baseline characteristics of study population by prenatal antibiotic exposure duration

| Baseline characteristics | Antibiotic exposure | | | $P^*$ | $P^\dagger$ |
|---|---|---|---|---|---|
| | None (n=52) | SD (n=35) | LD (n=58) | | |
| Mothers | | | | | |
| Maternal age (yr) | 35 (31, 38) | 32 (30, 35) | 32 (30, 35) | 0.045 | 0.930 |
| Cesarean delivery | 44 (84.6) | 21 (60.0) | 47 (81.0) | 0.018 | 0.027 |
| Multiple pregnancy | 5 (9.6) | 10 (28.6) | 17 (29.3) | 0.026 | 0.939 |
| IVF | 6 (11.5) | 4 (11.4) | 13 (22.4) | 0.211 | 0.184 |
| Histological chorioamnionitis | 6 (11.5) | 13 (37.1) | 29 (50.0) | <0.001 | 0.227 |
| PPROM (hr) | 0 (0) | 7 (0, 72) | 24 (0, 345) | <0.001 | 0.041 |
| GDM | 6 (11.5) | 1 (2.9) | 13 (22.4) | 0.025 | 0.014 |
| PIH | 25 (48.1) | 4 (11.4) | 4 (6.9) | <0.001 | 0.469 |
| Antenatal corticosteroids | 47 (90.4) | 34 (97.1) | 54 (93.1) | 0.475 | 0.647 |
| Infants | | | | | |
| GA (wk) | $30^{+5}$ ($29^{+0}$, $31^{+5}$) | $30^{+1}$ ($28^{+6}$, $31^{+2}$) | $28^{+0}$ ($25^{+3}$, $30^{+3}$) | <0.001 | 0.004 |
| GA <28 wk | 7 (13.5) | 6 (17.1) | 28 (48.3) | <0.001 | 0.003 |
| Male sex | 23 (44.2) | 12 (34.3) | 30 (51.7) | 0.260 | 0.102 |
| Small for GA | 11 (21.2) | 6 (17.1) | 3 (5.2) | 0.042 | 0.059 |
| Large for GA | 1 (1.9) | 1 (2.9) | 2 (3.6) | 0.874 | 0.853 |
| Birth weight (g) | 1,310 (957, 1,475) | 1,320 (1,020, 1,440) | 1,025 (780, 1,483) | 0.227 | 0.169 |
| Birth weight Z-score | −0.64 (−1.25, 0.22) | −0.04 (−0.62, 0.47) | 0.12 (−0.19, 0.62) | <0.001 | 0.057 |
| Length Z-score | −0.46 (−1.51, 0.31) | −0.14 (−0.87, 0.53) | −0.08 (−0.63, 0.45) | 0.040 | 0.824 |
| Head circumference Z-score | −0.43 (−1.16, 0.07) | −0.18 (−1.08, 0.34) | −0.17 (−0.74, 0.33) | 0.273 | 0.503 |
| Infants' antibiotic use | 49 (94.2) | 31 (88.6) | 56 (96.6) | 0.299 | 0.193 |
| Apgar score <7 at 5 min | 17 (32.7) | 14 (40.0) | 36 (62.1) | 0.006 | 0.039 |
| Feeding type | | | | 0.151 | 0.159 |
| Exclusive breast milk | 4/51 (7.8) | 4 (11.4) | 12/50 (24.0) | | |
| Exclusive formula milk | 1/51 (2.0) | 1 (2.9) | 0/50 (0.0) | | |
| Mixed feeding | 46/51 (90.2) | 30 (85.7) | 38/50 (76.0) | | |
| Duration of respiratory support (days) | 10 (5, 45) | 15 (5, 55) | 27 (6, 77) | 0.163 | 0.130 |
| TPN duration (days) | 11 (2, 19) | 9 (0, 29) | 13 (5, 37) | 0.287 | 0.192 |
| Δ Weight Z-score from admission to discharge | −0.42 (−0.70, −0.02) | −0.63 (−0.88, −0.35) | −0.41 (−0.86, −0.01) | 0.108 | 0.142 |
| Δ Length Z-score from admission to discharge | −0.75 (−1.10, −0.34) | −0.77 (−1.32, −0.29) | −0.89 (−1.59, −0.10) | 0.842 | 0.997 |
| Δ Head circumference Z-score from admission to discharge | −0.48 (−0.90, 0.19) | −0.72 (−1.34, −0.21) | −0.51 (−1.27, −0.02) | 0.262 | 0.325 |
| Length of hospital stay (days) | 50 (38, 77) | 56 (42, 76) | 55 (37, 100) | 0.865 | 0.953 |

Values are presented as median (interquartile range) or number (%).
Abbreviations: GA, gestational age; GDM, gestational diabetes mellitus; IVF, in vitro fertilization; LD, long-duration (>7 days); PIH, pregnancy-induced hypertension; PPROM, preterm prelabor rupture of the membranes; SD, short-duration (≤7 days); TPN, total parenteral nutrition
*Comparisons of the 3 groups (none vs. SD and LD); †Comparisons of the 2 groups (SD and LD).


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**Table 3.** Multiple linear regression analysis to evaluate the associated factors with birth weight-for-gestational age Z-score

| Factors | B | Standard error | β | *P*-value |
|---|---|---|---|---|
| Pregnancy-induced hypertension* | −0.553 | 0.181 | −0.244 | 0.003 |
| Cesarean delivery† | −0.652 | 0.173 | −0.287 | <0.001 |
| Long-duration of prenatal antibiotic exposure‡ | 0.501 | 0.149 | 0.258 | 0.001 |

*Adjusted for cesarean delivery, duration of prenatal antibiotic exposure, chorioamnionitis, preterm prelabor rupture of the membranes, maternal age, multiple pregnancy and gestational diabetes.
†Adjusted for duration of prenatal antibiotic exposure, pregnancy-induced hypertension, chorioamnionitis, preterm prelabor rupture of the membranes, maternal age, multiple pregnancy and gestational diabetes.
‡Adjusted for pregnancy-induced hypertension, cesarean delivery, chorioamnionitis, preterm prelabor rupture of the membranes, maternal age, multiple pregnancy and gestational diabetes.

PPROM duration, GDM, and PIH (beta: 0.258; standard error: 0.149; *P*<0.001) (**Table 3**), but the SD group did not. The length-for-GA and head circumference-for-GA Z-scores did not differ significantly among the 3 groups after the adjustment for confounders. There were no significant differences in sex, postnatal antibiotic administration rate, feeding type, duration of respiratory support and parenteral nutrition, change in Z-score of anthropometric measurements from birth to discharge, or length of hospital stay among the 3 groups.

### 3. Neonatal outcomes according to prenatal antibiotic exposure duration

After the adjustment for confounding variables with a value of *P*<0.1 for the baseline characteristics, the LD group was associated with higher adjusted odds ratio (aOR) of death (aOR, 8.926; 95% confidence interval [CI], 1.482–53.775) and composite outcome of death, NEC ≥ stage 2, and LOS (aOR, 2.375; 95% CI, 1.027–5.492) than the non-antibiotic group (**Table 4**). There were no significant differences in any neonatal outcomes between the non-antibiotic and SD groups or between the SD and LD groups. In the subgroup analysis of infants with PPROM, neonatal outcomes did not differ significantly between the SD and LD groups.

## DISCUSSION

This study found that LD prenatal antibiotic exposure was positively correlated with BW/GA Z-score. VP and VLBW infants in the LD group were associated with an increased risk of death and composite outcome of death, NEC, and LOS compared to the non-antibiotic group.

**Table 4.** Neonatal outcomes according to prenatal antibiotic exposure duration

| Outcome | Antibiotic exposure | | | SD vs. none* | LD vs. none* | LD vs. SD† |
|---|---|---|---|---|---|---|
| | None (n=52) | SD (n=35) | LD (n=58) | aOR‡ (95% CI) | aOR‡ (95% CI) | aOR§ (95% CI) |
| Death/NEC/LOS | 7 (13.5) | 10 (28.6) | 23 (39.7) | 4.229 (0.701–25.505) | 2.375 (1.027–5.492) | 0.563 (0.079–4.034) |
| Death/NEC/LOS/BPD/SNI/ROP | 18 (34.6) | 14 (40.0) | 36 (60.3) | 1.273 (0.282–5.754) | 1.043 (0.523–2.082) | 0.834 (0.112–6.206) |
| Death | 1 (1.9) | 2 (5.7) | 13 (22.4) | - | 8.926 (1.482–53.775) | 1.762 (0.106–29.170) |
| NEC ≥ stage 2 | 0 (0.0) | 3 (8.6) | 5 (8.6) | - | - | - |
| LOS | 7 (13.5) | 8 (22.9) | 13 (22.4) | 2.391 (0.507–11.273) | 1.213 (0.571–2.575) | 0.373 (0.052–2.656) |
| msBPD | 12/52 (23.1) | 9/34 (26.5) | 18/56 (32.1) | 4.343 (0.485–38.872) | 0.685 (0.330–1.421) | 0.582 (0.101–3.371) |
| SNI | 1 (1.9) | 2 (5.7) | 6 (10.3) | - | 1.989 (0.541–7.303) | 0.116 (0.001–10.465) |
| ROP ≥ stage 3 | 6/44 (13.6) | 2/24 (8.3) | 9/32 (28.1) | 0.162 (0.000–84.065) | 0.357 (0.063–2.028) | - |

Values are presented as number (%).
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; BPD, bronchopulmonary dysplasia; msBPD, moderate-to-severe bronchopulmonary dysplasia; LD, long-duration (>7 days); LOS, late-onset sepsis; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; SD, short-duration (≤7 days); SNI, severe neurologic injury (intraventricular hemorrhage [≥ grade III] or periventricular leukomalacia).
*Reference to the non-antibiotic group; †Reference to the SD group.
‡Adjusted for gestational age <28 weeks, maternal age, multiple pregnancy, cesarean delivery, gestational diabetes mellitus, histologic chorioamnionitis, duration of premature rupture of membrane, pregnancy-induced hypertension, small for gestational age, and Apgar score <7 at 5 minutes.
§Adjusted for gestational age <28 weeks, cesarean delivery, gestational diabetes mellitus, duration of premature rupture of membrane, maternal clarithromycin or ampicillin/sulbactam exposure, small for gestational age, and Apgar score <7 at 5 minutes.


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There were no significant differences in neonatal outcomes between the non-antibiotic and SD groups or between the SD and LD groups.

Antibiotic use in pregnancy is increasing.[2] In this study, the prescribed rate of prenatal antibiotics was 64%, higher than that in European countries or the US, which are reportedly 20–40%.[16] These differences are most likely due to differences in the study populations. Our study population was limited to VP or VLBW infants only, who would have many risk factors such as maternal PPROM, preterm labor, or chorioamnionitis. Therefore, the rate of prenatal antibiotic exposure of this population may be higher than that of all infants.

In our study, the most common indication for prenatal antibiotics was PPROM, which occurs in approximately 40% of all preterm deliveries.[17] Since the ORACLE study, antibiotics have been prescribed for mothers with PPROM to prolong pregnancy, reduce intrauterine infection, and prevent early-onset neonatal infection.[18] The ACOG guideline recommends a 7-day course of latency antibiotic therapy with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin.[5] Amoxicillin–clavulanic acid is not recommended due to increased rates of NEC. In our unit, the antibiotic regimen for PPROM was a combination of cephalosporins, clarithromycin, and metronidazole. The currently recommended antibiotics regimen varies in each country according to their randomized clinical trials.[19] There are several organisms in amniotic cavity and genital *Mycoplasmas* are the most frequent organisms invading the amniotic cavity in PPROM.[20] Genital *Mycoplasmas* display inherent resistance to beta-lactams and glycopeptides (e.g. vancomycin) because of the absence of a cell wall.[21] So previous Korean study designed a combination of antibiotic therapies for patients with PPROM, which was implemented in clinical practice in 2003 with the goal of providing antimicrobial activities to most organisms found in the amniotic cavity in PPROM.[19] They found out the administration of ceftriaxone, clarithromycin, and metronidazole was associated with a more successful eradication of intra-amniotic inflammation/infection and prevented secondary intra-amniotic inflammation/infection more frequently than an antibiotic regimen which included ampicillin and/or cephalosporins in patients with PPROM. Although clarithromycin is classified as pregnancy category C drug, it may be an appropriate candidate in treatment trials of genital *Mycoplasma* and *Ureaplasma* infections during pregnancy because of its enhanced placental passage compared with other macrolide antibiotics.[22] We adopted the regimen based on these previous studies.

While there is well-established evidence of an association between antibiotic exposure in early life and childhood overweight or obesity,[23] studies on the association of prenatal antibiotics with fetal growth have reported inconsistent results. Some studies reported an association with a lower BW,[24] while others reported an association with a higher BW.[25] In our study, LD prenatal antibiotic exposure was associated with a higher BW/GA Z-score. There are 2 possible explanations for this association. First, the intrauterine environment has been considered sterile, but recent studies indicated the presence of intrauterine microbes for infant gut colonization.[26,27] Antibiotics administered to pregnant women may impact the microbial gut colonization of offspring by disrupting the vertical bacterial transfer or via direct placental transfer of the antibiotics to the fetal circulation.[27,28] Changes in the fetal microbiota could alter the fetal metabolic systems, body composition, and growth,[29] similar to the mechanism by which antibiotics taken during infancy or childhood influence obesity.[30] Second, leptin and adiponectin have important roles ranging from endo/para/autocrine effects at the fetal–maternal interface to the regulation of conceptus development


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and fetal growth.[31] Mueller et al.[24] demonstrated that prenatal, especially third-trimester, antibiotic prescriptions were associated with cord blood levels of leptin and adiponectin in a dose-response fashion that have been positively correlated with fetal fat stores.[32] By this mechanism, prenatal antibiotics could only affect the fetus's weight, not its height and head circumference, as in our study. The effect of only LD, not SD, on BW in our study could be explained by the dose effect. Further studies are needed to evaluate the long-term metabolic effects of prenatal antibiotics on infants, children, and adults.

In our study, LD prenatal antibiotic exposure was associated with an increased risk of death and the composite outcome of death, NEC, and LOS compared to no antibiotic exposure despite the adjustment for many confounding factors, including GA, PPROM, histologic chorioamnionitis, PIH, and GDM. This result is inconsistent with that of Reed et al.,[10] who reported that prenatal antibiotic exposure had a protective effect on the combined outcome of NEC, sepsis, or death. The subjects of the previous study were mothers who had received antibiotics for a short period of time within 72 hours before delivery, but the LD group in our study received antibiotics for 8–47 days. These different durations of prenatal antibiotic exposure may have resulted in the different outcomes.

As mentioned above, prenatal antibiotic exposure may disturb the natural colonization and maturation of the infant microbiome via disrupted vertical bacterial transfer or via direct placental transfer of the antibiotics to the fetal circulation.[27,28] Studies in animal models have shown that prenatal antibiotic exposure results in reduced microbial diversity and/or population structure changes in the gut microbiota of the offspring.[33] Considering that important pathogenic factors for NEC are a premature gut and dysregulation of the microbiome/dysbiosis,[34] long-term exposure to prenatal antibiotics could increase the risk of NEC. Regarding the increased risk of sepsis due to prenatal antibiotic exposure, 2 mechanisms for this could be considered. First, early microbial gut colonization strongly influences immune system maturation.[35] Antibiotics may affect those processes, leading to persistent alterations in host immunity and increased immune-mediated diseases.[35] The animal study from Deshmukh et al.[36] showed that neonatal mice from dams exposed to prenatal antibiotics were associated with reduced circulating and bone marrow neutrophils, granulocyte/macrophage progenitor cells, and interleukin-17–producing cells in the intestine, which resulted in increased susceptibility to *E. coli* K1 and *Klebsiella pneumoniae* sepsis. Second, prenatal antibiotic exposure could increase the risk of antibiotic-resistant bacteria,[37] which could colonize in the neonates by vertical transmission.[38] Although early-onset sepsis caused by GBS has been reduced by intrapartum antibiotic prophylaxis, there has been an increasing trend of antibiotic-resistant GBS.[39] Conversely, there is also evidence that a reduction of prenatal antibiotic exposure reduces the rate of neonatal sepsis caused by antibiotic-resistant *E. coli*.[40] This evidence may support our results of poor outcomes in the LD group.

This study had several limitations. First, the small sample size limited our statistical analyses, which were unable to confirm the effects of prenatal antibiotics on NEC in the multivariate logistic regression analysis. Despite this limitation, prolonged prenatal antibiotic exposure has been identified as a risk factor for death or combined outcomes. Second, we did not analyze the effects of prenatal antibiotics based on antibiotic types or indications. However, the effects of these factors on outcomes could be excluded by adjusting these confounders.

In conclusion, prolonged prenatal antibiotic exposure could increase the BW/GA Z-score, risk of death, and composite outcome of death, NEC, and LOS in VP or VLBW infants. It is


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recommended that physicians prescribe prenatal antibiotics for an accurate duration with appropriate indications. Close monitoring of neonatal mortality and morbidities is necessary in cases of LD prenatal antibiotic exposure.

## REFERENCES

1. Bookstaver PB, Bland CM, Griffin B, Stover KR, Eiland LS, McLaughlin M. A review of antibiotic use in pregnancy. Pharmacotherapy 2015;35:1052-62.
PUBMED | CROSSREF
2. Broe A, Pottegård A, Lamont RF, Jørgensen JS, Damkier P. Increasing use of antibiotics in pregnancy during the period 2000-2010: prevalence, timing, category, and demographics. BJOG 2014;121:988-96.
PUBMED | CROSSREF
3. Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin No. 199: use of prophylactic antibiotics in labor and delivery. Obstet Gynecol 2018;132:e103-19.
PUBMED | CROSSREF
4. World Health Organization. WHO recommendations for prevention and treatment of maternal peripartum infections. Geneva: World Health Organization; 2015.
5. Prelabor rupture of membranes: ACOG practice bulletin, number 217. Obstet Gynecol 2020;135:e80-97.
PUBMED | CROSSREF
6. Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal *Escherichia coli* sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. Pediatrics 2008;121:689-96.
PUBMED | CROSSREF
7. Didier C, Streicher MP, Chognot D, Campagni R, Schnebelen A, Messer J, et al. Late-onset neonatal infections: incidences and pathogens in the era of antenatal antibiotics. Eur J Pediatr 2012;171:681-7.
PUBMED | CROSSREF
8. Weintraub AS, Ferrara L, Deluca L, Moshier E, Green RS, Oakman E, et al. Antenatal antibiotic exposure in preterm infants with necrotizing enterocolitis. J Perinatol 2012;32:705-9.
PUBMED | CROSSREF
9. Mercer BM, Miodovnik M, Thurnau GR, Goldenberg RL, Das AF, Ramsey RD, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. JAMA 1997;278:989-95.
PUBMED | CROSSREF
10. Reed BD, Schibler KR, Deshmukh H, Ambalavanan N, Morrow AL. The impact of maternal antibiotics on neonatal disease. J Pediatr 2018;197:97-103.e3.
PUBMED | CROSSREF
11. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
PUBMED | CROSSREF
12. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am 1986;33:179-201.
PUBMED | CROSSREF
13. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 2005;116:1353-60.
PUBMED | CROSSREF
14. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics 2005;116:595-602.
PUBMED | CROSSREF
15. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Chan RVP, Berrocal A, et al. International classification of retinopathy of prematurity, third edition. Ophthalmology 2021;128:e51-68.
PUBMED | CROSSREF
16. de Jonge L, Bos HJ, van Langen IM, de Jong-van den Berg LT, Bakker MK. Antibiotics prescribed before, during and after pregnancy in the Netherlands: a drug utilization study. Pharmacoepidemiol Drug Saf 2014;23:60-8.
PUBMED | CROSSREF
17. Kim SY, Kwon HS, Lee J, Sul AR, Ko HS, Yang JI. Questionnaire survey on the management of pregnant women with preterm premature rupture of membranes. Obstet Gynecol Sci 2020;63:286-92.
PUBMED | CROSSREF

18. Kenyon SL, Taylor DJ, Tarnow-Mordi W; ORACLE Collaborative Group. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. Lancet 2001;357:979-88.
PUBMED | CROSSREF

19. Lee J, Romero R, Kim SM, Chaemsaithong P, Yoon BH. A new antibiotic regimen treats and prevents intra-amniotic inflammation/infection in patients with preterm PROM. J Matern Fetal Neonatal Med 2016;29:2727-37.
PUBMED | CROSSREF

20. Oh KJ, Lee KA, Sohn YK, Park CW, Hong JS, Romero R, et al. Intraamniotic infection with genital mycoplasmas exhibits a more intense inflammatory response than intraamniotic infection with other microorganisms in patients with preterm premature rupture of membranes. Am J Obstet Gynecol 2010;203:211.e1-8.
PUBMED | CROSSREF

21. Redelinghuys MJ, Ehlers MM, Dreyer AW, Lombaard HA, Kock MM. Antimicrobial susceptibility patterns of *Ureaplasma* species and *Mycoplasma hominis* in pregnant women. BMC Infect Dis 2014;14:171.
PUBMED | CROSSREF

22. Park HS, Ahn BJ, Jun JK. Placental transfer of clarithromycin in human pregnancies with preterm premature rupture of membranes. J Perinat Med 2012;40:641-6.
PUBMED | CROSSREF

23. Aghaali M, Hashemi-Nazari SS. Association between early antibiotic exposure and risk of childhood weight gain and obesity: a systematic review and meta-analysis. J Pediatr Endocrinol Metab 2019;32:439-45.
PUBMED | CROSSREF

24. Mueller NT, Rifas-Shiman SL, Blaser MJ, Gillman MW, Hivert MF. Association of prenatal antibiotics with foetal size and cord blood leptin and adiponectin. Pediatr Obes 2017;12:129-36.
PUBMED | CROSSREF

25. Zhang M, Differding MK, Benjamin-Neelon SE, Østbye T, Hoyo C, Mueller NT. Association of prenatal antibiotics with measures of infant adiposity and the gut microbiome. Ann Clin Microbiol Antimicrob 2019;18:18.
PUBMED | CROSSREF

26. Collado MC, Rautava S, Aakko J, Isolauri E, Salminen S. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. Sci Rep 2016;6:23129.
PUBMED | CROSSREF

27. Nogacka AM, Salazar N, Arboleya S, Suárez M, Fernández N, Solís G, et al. Early microbiota, antibiotics and health. Cell Mol Life Sci 2018;75:83-91.
PUBMED | CROSSREF

28. Pacifici GM. Placental transfer of antibiotics administered to the mother: a review. Int J Clin Pharmacol Ther 2006;44:57-63.
PUBMED | CROSSREF

29. Dai Z, Wu Z, Hang S, Zhu W, Wu G. Amino acid metabolism in intestinal bacteria and its potential implications for mammalian reproduction. Mol Hum Reprod 2015;21:389-409.
PUBMED | CROSSREF

30. Mikkelsen KH, Allin KH, Knop FK. Effect of antibiotics on gut microbiota, glucose metabolism and body weight regulation: a review of the literature. Diabetes Obes Metab 2016;18:444-53.
PUBMED | CROSSREF

31. Nogues P, Dos Santos E, Jammes H, Berveiller P, Arnould L, Vialard F, et al. Maternal obesity influences expression and DNA methylation of the adiponectin and leptin systems in human third-trimester placenta. Clin Epigenetics 2019;11:20.
PUBMED | CROSSREF

32. Josefson JL, Zeiss DM, Rademaker AW, Metzger BE. Maternal leptin predicts adiposity of the neonate. Horm Res Paediatr 2014;81:13-9.
PUBMED | CROSSREF

33. Khan I, Azhar EI, Abbas AT, Kumosani T, Barbour EK, Raoult D, et al. Metagenomic analysis of antibiotic-induced changes in gut microbiota in a pregnant rat model. Front Pharmacol 2016;7:104.
PUBMED | CROSSREF

34. Andrews RE, Coe KL. Clinical presentation and multifactorial pathogenesis of necrotizing enterocolitis in the preterm infant. Adv Neonatal Care 2021;21:349-55.
PUBMED | CROSSREF

35. Zeissig S, Blumberg RS. Life at the beginning: perturbation of the microbiota by antibiotics in early life and its role in health and disease. Nat Immunol 2014;15:307-10.
PUBMED | CROSSREF

36. Deshmukh HS, Liu Y, Menkiti OR, Mei J, Dai N, O'Leary CE, et al. The microbiota regulates neutrophil homeostasis and host resistance to *Escherichia coli* K1 sepsis in neonatal mice. Nat Med 2014;20:524-30.
PUBMED | CROSSREF

37. Romagano MP, Fofah O, Swaminarayan D, Williams S, Apuzzio JJ, Gittens-Williams L. Maternal antepartum antibiotic administration and patterns of bacterial resistance in early preterm neonates. J Matern Fetal Neonatal Med 2020;1-5.
PUBMED | CROSSREF

38. Patangia DV, Ryan CA, Dempsey E, Stanton C, Ross RP. Vertical transfer of antibiotics and antibiotic resistant strains across the mother/baby axis. Trends Microbiol 2022;30:47-56.
PUBMED | CROSSREF

39. Hayes K, O'Halloran F, Cotter L. A review of antibiotic resistance in group B streptococcus: the story so far. Crit Rev Microbiol 2020;46:253-69.
PUBMED | CROSSREF

40. Doenhardt M, Seipolt B, Mense L, Winkler JL, Thürmer A, Rüdiger M, et al. Neonatal and young infant sepsis by group B streptococci and *Escherichia coli*: a single-center retrospective analysis in Germany-GBS screening implementation gaps and reduction in antibiotic resistance. Eur J Pediatr 2020;179:1769-77.
PUBMED | CROSSREF

## 요약

**목적:** 산모의 산전 항생제 사용은 여러가지 면에서 태아 및 신생아에 영향을 미칠 수 있다. 본 연구에서는 극소 미숙아 또는 극소 저체중출생아에서 산모의 산전 항생제 투여 기간이 신생아 예후에 미치는 영향에 대해 조사하였다.
**방법:** 2015년 9월부터 2020년 12월까지 고려대학교 안암병원에서 출생한 재태주수 32주 미만 또는 출생 체중 1,500 gram 미만인 신생아 및 산모를 대상으로 의무기록을 후향적으로 분석하였다. 산모의 산전 항생제 투여 기간에 따라 미투여 군, 7일 이하 군, 7일 초과 군의 세 군으로 나누어 산모의 특성, 환아의 특성 및 합병증 등을 비교 분석하였다.
**결과:** 총 145명 중 93명의 환아가 산전 항생제에 노출되었으며, 그 중 35명(37.6%)는 7일 이하 군, 58명(62.4%)는 7일 초과 군이었다. 7일 초과 군은 미투여 군에 비해 재태 연령에 따른 출생체중의 Z-score가 교란변수 보정 후에도 유의미하게 높았다(beta, 0.258; standard error, 0.149; P<0.001). 다변량 로지스틱 회귀 분석에서 7일 초과 군은 사망(adjusted odds ratio [aOR], 8.926; 95% confidence interval [CI], 1.482–53.775), 그리고 사망, 괴사성 장염, 후기 패혈증의 복합 평가 결과와 연관이 있었다(aOR, 2.375; 95% CI, 1.027–5.492).
**결론:** 산모의 장기간 산전 항생제 투여는, 극소 미숙아 또는 극소 저체중출생아에서 재태 연령에 따른 출생체중의 Z score을 증가시키며, 사망 뿐 아니라 사망, 괴사성 장염, 후기 패혈증의 복합 평가 결과의 위험도를 증가시킬 수 있다.