

The Relationship Between the Latency Period Observed in Late Preterm Prelabor Membrane Rupture and Outcomes Associated with Maternal and Neonatal Infection and Respiratory Morbidity: A Retrospective Cohort Study

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Abstract

Objective: To evaluate the association between the total latency period from membrane rupture to delivery in singleton pregnancies complicated by late preterm prelabor membrane rupture (PPROM) and clinical composite outcomes related to maternal infection, neonatal suspected infection/antibiotic-related composite outcomes, and neonatal respiratory composite outcomes.

Methods: This single-center retrospective cohort study included 218 women who gave birth at Ankara Etlik City Hospital between January 1, 2023, and May 31, 2026, and were diagnosed with late preterm PPRM at 34+0–36+6 weeks of gestation. The total observed latency was classified as <24 hours, 24–48 hours, or >48 hours. Composite outcomes were reconstructed from predefined recorded components. Groups were compared using Welch's one-way analysis of variance, the Kruskal–Wallis test, the chi-square test, or exact tests. Adjusted associations were estimated using Firth penalized logistic regression implemented with custom Python code. Continuous latency and the ≥ 72 -hour threshold were secondary, exploratory analyses. Since total latency is a measure completed at the time of delivery, the results were interpreted as associations with observed latency rather than as the causal effect of prolonging pregnancy.

Results: The latency period was <24 hours in 98 pregnancies, 24–48 hours in 62 pregnancies, and >48 hours in 58 pregnancies. Clinical composite outcomes associated with maternal infection were observed at rates of 7.1%, 11.3%, and 24.1%, respectively ($P=0.008$). After adjusting for gestational age at the time of PPRM, cervical dilation, C-reactive protein level at admission, Group B Streptococcus positivity, and nulliparity, a latency of >48 hours was associated with maternal composite outcomes (adjusted odds ratio [aOR] 6.83; 95% confidence interval [CI] 1.68–32.26; $P=0.006$). Neonatal suspected infection/antibiotic-related composite outcome was observed at rates of 11.2%, 11.3%, and 24.1%, respectively ($P=0.059$); the primary adjusted estimate for >48 hours was not statistically significant (aOR 2.73; 95% CI 0.79–10.12; $P=0.113$). An increase was observed in analyses of continuous latency and ≥ 72 hours; however, these were exploratory findings. Neonatal respiratory composite outcomes were observed at rates of 29.6%, 24.2%, and 15.5%, respectively, and showed no independent association with latency in the adjusted models. There were only three culture-positive cases of neonatal sepsis; no cases of maternal sepsis, maternal intensive care unit admission, or neonatal death were observed.

Conclusion: A latency period of >48 hours was associated with more severe clinical outcomes related to maternal infection; however, this finding does not indicate that intentionally prolonging pregnancy causes infection. The primary categorical analysis regarding neonatal infection was not statistically significant, and secondary signals were hypothesis-generating in nature. The latency period should not be used alone as an indication for delivery; it should be evaluated in conjunction with maternal-fetal findings, gestational age, cervical status, GBS, and treatment context.

Keywords: preterm prelabor membrane rupture; late preterm; latency period; intraamniotic infection; neonatal sepsis; respiratory morbidity

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Introduction

Preterm prelabor rupture of membranes (PPROM) is the rupture of the fetal membranes before labor begins and before 37 completed weeks of gestation. Late preterm PPRM occurs between 34+0 and 36+6 weeks. This period is a clinically

significant interval in which risks associated with prematurity—such as ascending infection, placental abruption, umbilical cord complications, and fetal distress—coexist. Major guidelines consider both delivery and carefully selected expectant

management to be acceptable options when the maternal and fetal conditions are stable. They emphasize that the decision should be made in consideration of gestational age, signs of infection, fetal assessment, Group B Streptococcus (GBS) status, and local neonatal resources (1–3).

Randomized trials have not identified a single superior strategy for all stable patients. In the PPRMT trial, immediate delivery following near-term PPRM did not significantly reduce neonatal sepsis; in contrast, respiratory morbidity was more common (4). Similarly, in the PPROMEXIL trial, labor induction between 34 and 37 weeks did not provide a clear benefit in terms of neonatal sepsis (5). A meta-analysis based on individual participant data showed that composite adverse neonatal outcomes were similar between immediate delivery and expectant management, although some maternal and secondary neonatal outcomes differed (6).

It is difficult to compare outcomes of infection because clinical definitions are not standardized. Maternal fever, fetal tachycardia, leukocytosis, uterine tenderness, and purulent or foul-smelling discharge may suggest a suspected intraamniotic infection; however, none of these findings alone is sufficiently specific. The Triple I framework has been proposed to distinguish between isolated fever and suspected or confirmed intrauterine infection/inflammation (7). Current guidelines note that suspected intraamniotic infection can sometimes be recognized even in the absence of fever when the clinical picture is strong (8). Neonatal infection is similarly complex; even if cultures are negative, clinical findings and risk assessment may warrant empirical antibiotic treatment (9). Therefore, composite outcomes involving antibiotic use reflect not only proven infection but also clinician behavior.

Respiratory morbidity presents a contrasting clinical challenge. Late preterm infants are at risk for transient neonatal tachypnea (TTN), respiratory distress syndrome (RDS), the need for oxygen or noninvasive respiratory support, and admission to the neonatal intensive care unit (NICU). Antenatal betamethasone reduces certain respiratory outcomes in selected pregnant women at risk for late preterm birth; however, delaying delivery solely to allow for full-term gestation may not be safe (10,11). Current neonatal respiratory guidelines support early noninvasive support and selective surfactant use; therefore, a broad respiratory composite outcome may reflect both the disease and clinical management (12).

Most studies compare planned immediate delivery with expectant management. In contrast, day-to-day clinical decisions are often based on the actual time elapsed since membrane rupture. The categories of <24 hours, 24–48 hours, and >48 hours correspond to practical time points used in

decisions regarding reevaluation, corticosteroid administration, laboratory monitoring, and induction. In previous cohorts, the association between longer latency and outcomes has varied depending on gestational age and the definition of outcome (13,14). In a recent multicenter Korean study, expectant management was associated with more cases of clinical neonatal sepsis, antibiotic use, and maternal inflammatory markers, while there was no increase in culture-positive neonatal sepsis, maternal sepsis, or neonatal death (15). This distinction highlights the need to evaluate clinical and management-based outcomes separately from proven infection. Furthermore, total latency is a measurement completed at the time of delivery; infection or fetal distress can accelerate delivery and shorten latency. Therefore, observed latency is not an outcome of a randomly assigned exposure or a direct management strategy.

Therefore, the association between predefined latency groups in late preterm PPRM and maternal infection-related clinical composite outcomes, neonatal suspected infection/antibiotic- e composite outcomes, and neonatal respiratory composite outcomes was evaluated. The hypothesis was formulated that longer observed latency would be associated with maternal clinical composite outcomes. It was anticipated that any potential benefit regarding respiratory outcomes would be strongly influenced by gestational age, cervical status at presentation, and treatment opportunities. The analyses were designed to evaluate associations with total completed latency rather than to assess the causal effect of the pregnancy prolongation strategy.

Methods

Study Design and Setting

This retrospective, single-center cohort study was conducted at the Perinatology Department of Ankara Etlik City Hospital. Electronic maternal, delivery, laboratory, and neonatal records from January 1, 2023, to May 31, 2026, were reviewed. The report was prepared in accordance with the STROBE guidelines for observational cohort studies (16). No additional examinations, laboratory tests, imaging, treatments, or patient contact were performed. The study protocol was approved by the Scientific Research Evaluation and Ethics Committee of Ankara Etlik City Hospital on June 30, 2026 (approval no. AEŞH-BADEK2-2026-535).

Participants

Eligible participants were women aged 18 years and older with a singleton pregnancy who were diagnosed with PPRM between 34+0 and 36+6 weeks of gestation. Gestational age was determined based on the last menstrual period and/or first-trimester ultrasound. Membrane rupture was documented by clinical history, sterile speculum examination, visible amniotic fluid leakage, and, in

cases of uncertain diagnosis, biochemical confirmation. Follow-up, delivery, and neonatal care were conducted at the study center, and baseline maternal-neonatal outcome data were required. Exclusion criteria included PPROM occurring at $<34+0$ or $\geq 37+0$ weeks, multiple gestation, major fetal structural or chromosomal anomalies, and delivery outside the study hospital. Patients presenting with clinical chorioamnionitis, placental abruption, severe fetal distress, placenta previa, severe preeclampsia or HELLP syndrome, severe fetal growth restriction, active systemic infection, active COVID-19, or any other condition requiring urgent delivery unrelated to PPROM were also excluded.

Definition of exposure

The observed total latency period was defined as the interval, in hours, between the time of reported or documented membrane rupture and delivery. Primary exposure was categorized into three groups as predefined: <24 hours, 24–48 hours, and >48 hours; <24 hours was the reference category. In secondary analyses, latency was assessed continuously in 24-hour increments and using a predefined threshold of ≥ 72 hours. The protocol also allowed for the classification of latency >48 hours into the subgroups 48 hours– <7 days and ≥ 7 days. Since the maximum latency was 138.4 hours, no participant reached 7 days, and therefore no subgroup analysis was performed for this group. Because total latency is a measure completed at the time of delivery and influenced by clinical course, the regression results were not interpreted as indicating a causal effect of prolonging pregnancy.

Variables and outcome definitions

The recorded maternal and presentation variables included maternal age, body mass index, nulliparity, smoking during pregnancy, previous cesarean section, gestational age at the time of PPROM, cervical dilation, white blood cell count, C-reactive protein (CRP), GBS status, antenatal corticosteroids, and antibiotic use during the latent phase. GBS was dichotomously coded as positive or not documented as positive (negative/unknown). In the analytical dataset, antibiotics during the latent phase were recorded only as present/absent; the specific drug, dose, start time, duration, and indications for prophylaxis versus treatment could not be distinguished. Obstetric variables included induction, mode of delivery, cesarean section due to an abnormal fetal heart rate pattern, clinical chorioamnionitis, maternal fever, elevated inflammatory markers triggering further evaluation, postpartum endometritis, postpartum hemorrhage, maternal sepsis, and intensive care unit admission. Neonatal variables included birth weight, sex, Apgar scores, umbilical artery pH, NICU admission and length of stay, TTN, RDS, respiratory support, continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC), mechanical

ventilation, surfactant, neonatal antibiotics, clinically and culture-confirmed sepsis, and death.

Primary and secondary outcomes

The clinical composite outcome associated with maternal infection was composed of the following predefined components: clinical chorioamnionitis; maternal fever during the latent period or intrapartum; elevated CRP or white blood cell count triggering further clinical evaluation; postpartum endometritis; or maternal sepsis/admission to the intensive care unit. Since there was no single numerical threshold applied to all cases for the CRP/WBC component in the structured data, this variable was defined based on the clinician's decision to trigger further evaluation as recorded in the charts. The neonatal suspected infection/antibiotic composite outcome included clinical neonatal sepsis, culture-positive sepsis, or neonatal antibiotic treatment due to suspected infection. These two broad categories were interpreted not as confirmed infection outcomes but as infection-related clinical findings and care processes; clinical chorioamnionitis, culture-positive neonatal sepsis, and serious events were also reported. The neonatal respiratory composite outcome included TTN, RDS, any respiratory support (CPAP or HFNC), mechanical ventilation, or surfactant administration. Since respiratory disease was not coded as a separate primary indication for NICU admission in the dataset, general NICU admission was not included in the composite and was retained as a secondary outcome. Other secondary outcomes included induction, cesarean delivery, a 5-minute Apgar score <7 , umbilical artery pH <7.10 , NICU length of stay, postpartum hemorrhage, severe maternal morbidity, and neonatal death.

Data quality and missing data

The analytical dataset contained a single row for each pregnancy, and no duplicate rows were detected. The recorded latency groups were consistent with the continuous latency values. Three composite endpoints and the umbilical artery pH <7.10 indicator were deterministically reconstructed from the predefined components; the existing summary fields were not included in the analysis. Six summary markers did not match the values derived from the components, but the underlying components were not altered. There were no missing values in the primary analysis variables. The NICU length of stay was available for all 77 infants admitted to the NICU (); it was structurally missing for the 141 infants not admitted. No imputation was performed, and length of stay was analyzed only among infants admitted to the NICU.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation or median (interquartile range) when appropriate, and categorical variables were

summarized as counts and percentages. The distribution pattern was assessed through graphical examination and the Shapiro–Wilk test. Continuous variables across the three latency groups were compared using Welch’s one-way analysis of variance or the Kruskal–Wallis test. For categorical variables, the Pearson chi-square test was used, or the Fisher–Freeman–Halton exact test when expected cell counts were low. Pairwise comparisons were performed only after a significant overall test and were corrected using the Holm method.

Regression and sensitivity analyses

Since the number of events in the primary endpoints was limited and some cells were sparse, Firth-penalized logistic regression was used. Firth estimates were calculated using custom Python code based on the Jeffreys prior, penalized likelihood, and modified score equations; 95% profile penalized likelihood confidence intervals and likelihood ratio P-values were obtained for the latency terms (17). Primary models were constructed using variables available at or immediately after the onset of PPROM. Models associated with maternal and neonatal infection were adjusted for gestational age at the time of PPROM, cervical dilation, admission CRP (per 10 mg/L increase), GBS positivity, and nulliparity. The respiratory model used neonatal sex instead of nulliparity.

In secondary sensitivity analyses, latency was modeled as continuous in 24-hour increments and as <72 hours versus ≥72 hours. In exploratory models including management variables, the following were used for maternal outcomes: gestational age at the time of PPROM, cervical dilation, CRP, GBS positivity, and latency to antibiotic administration; for outcomes related to neonatal infection: gestational age at birth, antenatal corticosteroids, latency to antibiotic administration, GBS positivity, and cesarean delivery; and for respiratory outcomes, gestational age at delivery, antenatal corticosteroids, cesarean delivery, birth weight, and neonatal sex were used. Since some of these variables may arise after the latency period, the models were interpreted as direct association analyses rather than adjustments for causal confounders. No multiple-test correction was applied for secondary and sensitivity analyses; the results were considered hypothesis-generating.

Software and Reproducibility

The analyses were performed using Python 3.13.5 (Python Software Foundation), pandas 2.2.3, NumPy 2.3.5, and SciPy 1.17.0. The code reproducing the Firth application and the results in Tables 4–5 is provided in Supplementary File 1. All tests were two-tailed, and a $P < 0.05$ threshold was used for statistical significance in the primary analyses.

Results

Cohort and latency duration distribution

The analytical cohort included 218 singleton pregnancies with late preterm PPROM. The latency was <24 hours in 98 pregnancies (45.0%), 24–48 hours in 62 pregnancies (28.4%), and >48 hours in 58 pregnancies (26.6%). The overall median latency was calculated as 30.1 hours (interquartile range 12.4–63.1). The group medians were 12.1, 35.2, and 89.1 hours, respectively ($P < 0.001$). The longest latency was 138.4 hours. There were no missing values for the outcome and adjustment variables.

Onset and Treatment Characteristics

Maternal age, body mass index, nulliparity, smoking status, previous cesarean section, white blood cell count at admission, C-reactive protein (CRP) level at admission, and GBS positivity were similar across the latency groups (Table 1). The mean gestational age at the time of PPROM was 35.49 ± 0.66 , 35.30 ± 0.63 , and 35.23 ± 0.60 weeks in the <24, 24–48, and >48-hour groups, respectively ($P = 0.027$). Cervical dilation at admission was 2.5 (2.0–3.0), 1.0 (0.5–1.5), and 0.5 (0.5–1.0) cm, respectively ($P < 0.001$). The use of antenatal corticosteroids increased from 35.7% to 54.8% and 72.4% ($P < 0.001$). Antibiotic use during the latency period was 86.7% overall and did not differ significantly between groups. In Holm-corrected pairwise comparisons, differences in gestational age at the time of PPROM were concentrated between the <24 and >48-hour groups; cervical dilation, however, differed across all pairwise comparisons. These initial differences served as significant sources of confounding for the observed associations between latency and outcomes.

Maternal and Obstetric Outcomes

Labor induction became more common as the latency period increased, with rates of 44.9%, 62.9%, and 69.0% in the groups, respectively ($P = 0.007$). Cesarean section rates were 30.6%, 25.8%, and 25.9% ($P = 0.737$). Clinical chorioamnionitis was 2.0% in the <24-hour group and rose to 12.1% in the >48-hour group ($P = 0.032$). Maternal fever increased from 3.1% to 15.5% ($P = 0.013$), and elevated CRP/WBC levels—which triggered further evaluation—rose from 6.1% to 24.1% ($P = 0.004$). Clinical composite outcomes related to maternal infection were observed in 7 of 98 women (7.1%), 7 of 62 women (11.3%), and 14 of 58 women (24.1%) ($P = 0.008$) (Table 2). There were no cases of maternal sepsis or intensive care unit admission. Holm-corrected pairwise comparisons showed that the >48-hour group differed from the <24-hour group in terms of chorioamnionitis, fever, elevated inflammatory markers, and maternal clinical composite outcomes. Postpartum hemorrhage and endometritis were rare

and did not show significant differences between the groups.

Newborn Results

The mean birth weight was 2657 ± 325 g and did not differ among the latency groups. NICU admission rates were 38.8%, 35.5%, and 29.3%, respectively ($P=0.489$). The length of stay in the NICU differed among the groups ($P=0.005$); the median durations were 5, 3, and 5 days, respectively. No significant differences were observed regarding TTN, RDS, respiratory support, low Apgar score, or umbilical artery pH <7.10 (Table 3). The rates of suspected neonatal infection/antibiotic treatment were 11.2%, 11.3%, and 24.1%, respectively ($P=0.059$). The rates of neonatal respiratory composite outcomes were 29.6%, 24.2%, and 15.5% ($P=0.141$). Culture-positive neonatal sepsis was detected in only three infants, and no neonatal deaths occurred. Maternal and neonatal composite outcomes were not the same variable at the patient level; both composites were present together in only five mother-infant pairs. The overall difference in NICU length of stay stemmed from the comparison between the <24 -hour and 24–48-hour groups; no consistent prolongation was observed in the >48 -hour group.

Primary adjusted analyses

In the primary Firth model, a latency of >48 hours was associated with a clinical composite outcome related to maternal infection compared with <24 hours (aOR 6.83; 95% CI 1.68–32.26; $P=0.006$). The comparison between 24 and 48 hours was not significant (aOR 2.68; 95% CI 0.72–10.47; $P=0.141$). The estimate for >48 hours for neonatal suspected infection/antibiotic-related composite outcome was high but uncertain and was not statistically significant in the primary analysis (aOR 2.73; 95% CI 0.79–10.12; $P=0.113$). Neither latency category showed an independent association with neonatal respiratory outcome; the aOR for >48 hours was 0.63 (95% CI 0.21–1.87; $P=0.410$) (Table 4).

Sensitivity and exploratory analyses

When maternal clinical composite outcome was modeled as a continuous latent variable, the aOR was 1.53 (95% CI 1.10–2.16; $P=0.012$) per 24-hour increase, and in the analysis comparing <72 hours to ≥ 72 hours, the aOR was 3.67 (95% CI 1.32–10.81; $P=0.012$). The association with >48 hours persisted in an exploratory model that included latency to antibiotic administration and selected baseline variables (aOR 7.95; 95% CI 1.88–39.89; $P=0.004$). Neonatal suspected infection/antibiotic regimen outcome showed an aOR of 1.47 (95% CI 1.08–2.03; $P=0.015$) per 24 hours in the continuous model and an aOR of 3.10 (95% CI 1.16–8.56; $P=0.024$) in the ≥ 72 -hour analysis. However, the categorical comparison for >48 hours was not significant when adjusted for gestational age at birth and management variables (aOR 1.93; 95% CI 0.77–4.91; $P=0.160$). Neonatal respiratory

composite outcome was not associated with continuous or ≥ 72 -hour latency (Table 5). Since no multiple-test correction was applied in these secondary analyses, the findings were interpreted as exploratory.

Discussion

This study revealed three main findings. First, the clinical composite outcome associated with maternal infection increased across latency groups and persisted after adjusting for presentation characteristics in cases with observed latency of >48 hours. However, since total latency is a measure completed at the time of delivery, this association does not indicate that prolongation of pregnancy causes infection. Second, the predefined >48 -hour category for neonatal suspected infection/antibiotic-related composite outcome () was not significant in the primary model; continuous latency and ≥ 72 -hour outcomes only yielded an exploratory signal. Third, the reduction in crude respiratory rate observed with longer latency was not independent after adjustment. The findings do not support reducing the decision regarding late preterm PPRM to a single fixed-time rule.

The results are generally consistent with randomized evidence regarding the timing of delivery. In the PPROMT and PPROMEXIL studies, routine immediate delivery did not significantly reduce neonatal sepsis; however, it did increase certain respiratory outcomes associated with prematurity (4,5). A meta-analysis based on individual participant data also showed that composite adverse neonatal outcomes were similar between immediate delivery and expectant management, although some secondary maternal and neonatal outcomes differed (6). The PPROMEXIL-2 trial and the Cochrane review support the finding that while planned early delivery may reduce certain maternal infection outcomes, it may increase prematurity-related morbidity, and that there is no single universally superior strategy (18,19). Our study differs from these by examining the total latency period rather than the assigned management strategy.

Cohorts focusing on latency have also reported heterogeneous results. Frenette et al. demonstrated that maternal and neonatal outcomes differed across clinically interpretable latency intervals (13). Choi et al. reported that prolonged latency was not necessarily harmful in carefully selected and monitored cases of late preterm PPRM (14). Drassinower and colleagues found no independent association between prolonged latency and neonatal sepsis when gestational age was taken into account (20). Müller and colleagues also emphasized that neonatal outcome is strongly influenced not only by the elapsed time but also by prematurity and the clinical context (21). Data from earlier gestational weeks indicate that the

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prognostic significance of latency depends on gestational age and the definition of outcome (22).

The maternal finding is biologically plausible; rupture of the membranes removes the mechanical barrier against ascending microorganisms, and cumulative exposure may increase over time. However, our conclusion was not a culture-confirmed infection, but rather a broad complex involving clinical and management-based factors. While a longer total latency period allows more time for inflammatory findings to become apparent, suspicion of infection can terminate the latency by accelerating delivery. This bidirectional relationship cannot be disentangled using standard logistic regression. Therefore, the finding does not indicate that prolonging the wait causes infection, but rather that a longer observed latency is associated with more clinical events related to infection. The absence of maternal sepsis and intensive care unit admission should also be noted. Furthermore, there were only 28 maternal events, and the model included multiple covariates; the wide confidence interval for the >48-hour estimate indicates that the exact magnitude of the association cannot be determined.

Neonatal outcomes should be interpreted with even greater caution. The crude incidence rate increased in the >48-hour group; however, the primary categorical estimate had a wide confidence interval and did not reach statistical significance. Although the analyses of continuous latency and ≥ 72 hours yielded significant results, these were secondary, unadjusted for multiple testing, and hypothesis-generating analyses. The most common components of the composite outcome were neonatal antibiotic use and clinical sepsis; only three infants had culture-positive sepsis. Clinicians may investigate and treat the newborn more frequently in the presence of prolonged membrane rupture or maternal inflammatory findings, even if cultures remain negative. Therefore, the composite outcome reflects not only microbiological infection but also clinician behavior and antibiotic management. A similar distinction between clinical neonatal sepsis and antibiotic use versus culture-positive sepsis has been reported in a multicenter study from Korea (15).

Respiratory findings should not be interpreted as evidence that a longer latency period is protective. Cervical dilation was greater in patients who delivered within the first 24 hours; this suggests more advanced labor and a lower likelihood of continuing the pregnancy. Exposure to antenatal corticosteroids was also significantly associated with longer latency. These differences introduce confounding factors related to indication and clinical opportunity. Adjusted models did not show an independent respiratory benefit. This result is consistent with the central role of gestational age

and modern respiratory management in the risk of TTN and RDS (10–12).

The practical interpretation of the findings is that a long latency period is not an automatic indication for delivery but rather a context for clinical reevaluation. Repeated assessment of fever, uterine tenderness, fetal heart rate, vaginal discharge, and trends in inflammatory markers may be important; however, the elapsed time alone should not override stable maternal and fetal findings. The antibiotic variable in our study was recorded only as present/absent, and it was not possible to distinguish between prophylactic use and therapeutic use of GBS prophylaxis. A recent cohort study of late preterm births directly compared cases with and without latency-period antibiotic administration (23). ORACLE I, on the other hand, demonstrated the benefit of erythromycin-based treatment in earlier PPRM (24). These different clinical contexts highlight the importance of distinguishing antibiotic exposure based on drug, timing, duration, and indication, rather than interpreting it as a single, uniform variable.

The study has several strengths. The cohort was limited to a clinically consistent range of late preterm births. Outcomes related to maternal infection, neonatal infection, and respiratory outcomes were examined separately rather than being combined under a single broad adverse outcome category. Initial cervical dilation and CRP were included in the primary models. Composite outcomes were deterministically reconstructed from their components, and rare events were assessed using Firth regression. Sharing the specific analysis code enhanced the reproducibility of the results. Analyses of continuous variables and those lasting ≥ 72 hours exploratively assessed the dependence of the findings on a single categorization.

Limitations are important. A retrospective design cannot eliminate confounding factors arising from indications, clinician selection, and changes in treatment over time. The time of rupture was based in part on patient reports. Clinical chorioamnionitis, clinical neonatal sepsis, and elevated CRP/WBC levels triggering further evaluation may have varied according to records and clinician decisions; there was no single numerical threshold for this last component in the structured data. Because infection-related components included elements of the treatment and care process, their specificity for confirmed infection was limited. GBS-negative cases could not be distinguished from cases of unknown status. Information on the antibiotic type, dose, start time, duration, and indication was not available. Histological placental inflammation and the primary cause of admission to the neonatal intensive care unit (NICU) were not included in the structured data.

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Total latency was defined as the duration of follow-up completed at the time of delivery; since infection or fetal distress can shorten latency by accelerating delivery, there are issues regarding time-at-risk and reverse causality. Because the onset time of infection was not recorded, a time-stratified analysis could not be performed. The number of events was limited relative to the model complexity, and the confidence intervals were wide. There was no screening log showing the number and reasons for excluded records. The single-center design limited external validity; multiple-test correction and external validation were not performed in the secondary analyses.

Future studies should use standardized definitions of maternal and neonatal infections; the onset of infection and the indication for delivery should be prospectively recorded; and prophylactic antibiotics, GBS prophylaxis, and antibiotics administered for therapeutic purposes should be distinguished from one another. Analyses that account for changing exposure patterns over time, treat infection-free birth as a competing event, or use predefined landmark analyses may better assess the bidirectional relationship between the latency period and clinical events than standard logistic regression. Results must be validated in independent cohorts before any latency threshold is used for decision support.

Conclusion

In 218 singleton pregnancies with late preterm PPRM, the observed total latency of >48 hours was associated with clinical composite outcomes related to maternal infection after adjusting for gestational age at the time of PPRM, cervical dilation, CRP level at admission, GBS positivity, and nulliparity. However, total latency is a measure completed at the time of delivery and influenced by clinical course; this analysis does not demonstrate that intentionally prolonging pregnancy causes infection. Neonatal suspected infection/antibiotic-related composite outcome did not show an independent association with the predefined >48-hour category in the primary model. Increases in continuous latency and analyses at ≥ 72 hours were exploratory and hypothesis-generating in nature. The decrease in raw respiratory rate observed with longer latency was also not independent. No cases of maternal sepsis, maternal intensive care unit admission, or neonatal death were observed. These findings do not support a mandatory 48- or 72-hour delivery threshold. The latency period should be evaluated in conjunction with gestational age, cervical status, maternal inflammatory markers, fetal assessment, GBS, exposure to treatment, and local neonatal capacity; prolonged latency should be used as a context for closer clinical monitoring.

Author Contributions:

Emel Ozalp (EO): Conceptualization, methodology, investigation, formal analysis, and writing—original draft.

Kubilay Canga (KC): Methodology, data collection, and investigation.

Ozgun Volkan Akbulut (OVA): Investigation, data collection, data curation, and writing—review and editing.

Bengisu Elustu (BE): Investigation, data collection, and data curation.

Berkay Amac (BA): Data collection, and formal analysis.

Recep Taha Agaoglu (RTA): Investigation, data collection, and writing—review and editing.

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Informed Consent Statement: The requirement for informed consent was waived by the Institutional Review Board because of the retrospective design of the study and the use of anonymized patient data.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available because of patient privacy and ethical restrictions.

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Conflicts of Interest: The authors declare no conflicts of interest.

Use of artificial intelligence: Artificial intelligence was used to edit the English language and check the reference formatting; subsequently, all changes were reviewed by the authors. The authors bear full responsibility.

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Tables

Table 1. Maternal, presentation, and treatment characteristics by latency group

Variable	Total (n=218)	<24 hours (n=98)	24–48 hours (n=62)	>48 hours (n=58)	P- value
Latency period, hours	30.1 (12.4–63.1)	12.1 (9.6–15.3)	35.2 (31.1–38.9)	89.1 (74.6–98.6)	<0.001
Maternal age, years	29.9 ± 4.9	29.8 ± 5.0	30.4 ± 4.7	29.7 ± 5.0	0.681
Women who have not given birth	101 (46.3)	45 (45.9)	29 (46.8)	27 (46.6)	0.994
Body mass index, kg/m ²	27.4 (25.1–30.1)	26.9 (24.9–29.9)	27.4 (25.3–29.7)	27.9 (25.0–30.7)	0.753
Smoking during pregnancy	24 (11.0)	11 (11.2)	7 (11.3)	6 (10.3)	0.982
Previous cesarean delivery	31 (14.2)	13 (13.3)	9 (14.5)	9 (15.5)	0.924
Gestational age at the time of PPRM, weeks	35.37 ± 0.64	35.49 ± 0.66	35.30 ± 0.63	35.23 ± 0.60	0.027
Cervical dilation at hospital admission, cm	1.5 (1.0–2.5)	2.5 (2.0–3.0)	1.0 (0.5–1.5)	0.5 (0.5–1.0)	<0.001
WBC at hospital admission, ×10 ⁹ /L	11.5 ± 3.1	11.3 ± 3.0	11.3 ± 3.1	11.8 ± 3.3	0.672
CRP at hospital admission, mg/L	8.6 (4.5–16.6)	9.0 (4.8–16.9)	7.5 (4.5–13.4)	9.8 (4.4–22.4)	0.251
GBS-positive	18 (8.3)	7 (7.1)	5 (8.1)	6 (10.3)	0.776
Antenatal corticosteroids	111 (50.9)	35 (35.7)	34 (54.8)	42 (72.4)	<0.001
Antibiotic use during the latent period	189 (86.7)	80 (81.6)	55 (88.7)	54 (93.1)	0.107
Gestational age at birth, weeks	35.60 ± 0.65	35.58 ± 0.66	35.50 ± 0.62	35.75 ± 0.63	0.091

Values are presented as mean ± standard deviation, median (interquartile range), or n (%). Continuous variables were compared using Welch's one-way analysis of variance or the Kruskal–Wallis test; categorical variables were compared using Pearson's chi-square test

or the Fisher–Freeman–Halton exact test. The GBS variable was dichotomously coded as positive or not documented as positive (negative/unknown). Abbreviations: CRP, C-reactive protein; GBS, Group B Streptococcus; PPRM, preterm prelabor membrane rupture; WBC, white blood cell count.

Table 2. Maternal and obstetric outcomes by latency group

Variable	Total (n=218)	<24 hours (n=98)	24–48 hours (n=62)	>48 hours (n=58)	P- value
Labor induction	123 (56.4)	44 (44.9)	39 (62.9)	40 (69.0)	0.007
Vaginal delivery	157 (72.0)	68 (69.4)	46 (74.2)	43 (74.1)	0.737
Cesarean delivery	61 (28.0)	30 (30.6)	16 (25.8)	15 (25.9)	0.737
Cesarean section due to an abnormal fetal heart rate pattern	24 (11.0)	13 (13.3)	6 (9.7)	5 (8.6)	0.619
Clinical chorioamnionitis	12 (5.5)	2 (2.0)	3 (4.8)	7 (12.1)	0.032
Maternal fever during the latent phase or intrapartum	15 (6.9)	3 (3.1)	3 (4.8)	9 (15.5)	0.013
Elevated CRP/WBC levels triggering further evaluation	27 (12.4)	6 (6.1)	7 (11.3)	14 (24.1)	0.004
Postpartum endometritis	7 (3.2)	1 (1.0)	2 (3.2)	4 (6.9)	0.112
Clinical composite outcome associated with maternal infection	28 (12.8)	7 (7.1)	7 (11.3)	14 (24.1)	0.008
Postpartum hemorrhage	9 (4.1)	4 (4.1)	2 (3.2)	3 (5.2)	0.831
Maternal sepsis or intensive care admission	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	None

Values are given as n (%). Clinical composite outcome associated with maternal infection includes clinical chorioamnionitis, maternal fever during the latent period or intrapartum, elevated CRP/WBC levels triggering further evaluation, postpartum endometritis, or maternal sepsis/intensive care admission. This broad composite reflects not a confirmed infection, but infection-related clinical findings and care processes. Abbreviations: CRP, C-reactive protein; WBC, white blood cell count.

Table 3. Neonatal Outcomes by Latent Group

Variable	Total (n=218)	<24 hours (n=98)	24–48 hours (n=62)	>48 hours (n=58)	P-value
Birth weight, g	2657±325	2,649 ± 345	2678 ± 284	2647 ± 334	0.810
Male	112 (51.4)	51 (52.0)	31 (50.0)	30 (51.7)	0.967
5-minute Apgar score	9 (8–9)	9 (8–9)	9 (8–9)	9 (8–9)	0.556
5-minute Apgar score <7	6 (2.8)	3 (3.1)	2 (3.2)	1 (1.7)	1.000
Umbilical artery pH	7.240 ± 0.061	7.243 ± 0.054	7.244 ± 0.064	7.230 ± 0.069	0.416
Umbilical artery pH <7.10	7 (3.2)	2 (2.0)	3 (4.8)	2 (3.4)	0.626
YYBÜ admission	77 (35.3)	38 (38.8)	22 (35.5)	17 (29.3)	0.489
Length of stay at YYBÜ, days*	4 (3–6)	5 (4–6)	3 (2–5)	5 (2–6)	0.005
Transient neonatal tachypnea	42 (19.3)	22 (22.4)	12 (19.4)	8 (13.8)	0.416
Respiratory Distress Syndrome	17 (7.8)	10 (10.2)	5 (8.1)	2 (3.4)	0.322
Any respiratory support	38 (17.4)	21 (21.4)	11 (17.7)	6 (10.3)	0.211
CPAP or HFNC	30 (13.8)	17 (17.3)	9 (14.5)	4 (6.9)	0.183
Mechanical ventilation	4 (1.8)	2 (2.0)	1 (1.6)	1 (1.7)	1,000
Surfactant application	7 (3.2)	4 (4.1)	2 (3.2)	1 (1.7)	0.887
Neonatal antibiotic therapy	31 (14.2)	11 (11.2)	7 (11.3)	13 (22.4)	0.114
Clinical neonatal sepsis	25 (11.5)	8 (8.2)	6 (9.7)	11 (19.0)	0.107
Culture-positive neonatal sepsis	3 (1.4)	0 (0.0)	1 (1.6)	2 (3.4)	0.101

Variable	Total (n=218)	<24 hours (n=98)	24–48 hours (n=62)	>48 hours (n=58)	P-value
Suspected neonatal infection/antibiotic regimen completion	32 (14.7)	11 (11.2)	7 (11.3)	14 (24.1)	0.059
Neonatal respiratory composite outcome	53 (24.3)	29 (29.6)	15 (24.2)	9 (15.5)	0.141
Neonatal death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	None

*The length of stay in the NICU was analyzed only among the 77 infants admitted (total n=77; <24 hours, n=38; 24–48 hours, n=22; >48 hours, n=17). Neonatal suspected infection/antibiotic outcome includes clinical neonatal sepsis, culture-positive sepsis, or antibiotic treatment for suspected infection, and may be influenced by care decisions. Respiratory outcome includes TTN, RDS, any respiratory support, CPAP/HFNC, mechanical ventilation, or surfactant. Abbreviations: CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; RDS, respiratory distress syndrome; TTN, transient neonatal tachypnea; NICU, neonatal intensive care unit.

Table 4. Primary Firth-adjusted logistic regression models

Conclusion	Latent contrast	Number of events/n	Adjusted odds ratio	95% confidence interval	P-value
Clinical composite outcome associated with maternal infection	24–48 hours vs. <24 hours	28/218	2.68	0.72–10.47	0.141
Clinical composite outcome associated with maternal infection	>48 hours vs. <24 hours	28/218	6.83	1.68–32.26	0.006
Suspected neonatal infection/antibiotic regimen completion	24–48 hours vs. <24 hours	32/218	0.95	0.29–3.10	0.933
Suspected neonatal infection/antibiotic regimen completion	>48 hours vs. <24 hours	32/218	2.73	0.79–10.12	0.113
Neonatal respiratory composite outcome	24–48 hours vs. <24 hours	53/218	0.89	0.36–2.19	0.805
Neonatal respiratory composite outcome	>48 hours vs. <24 hours	53/218	0.63	0.21–1.87	0.410

Models associated with maternal and neonatal infection were adjusted for gestational age at the time of PPRM, cervical dilation at admission, CRP at admission (per 10 mg/L increase), GBS positivity, and nulliparity. The respiratory model used neonatal sex instead of nulliparity. The estimates show associations with observed total latency and should not be interpreted as a causal effect of prolonging pregnancy. Profile-penalized likelihood confidence intervals and likelihood ratio P-values are provided for latency terms. Abbreviations: aOR, adjusted odds ratio; CRP, C-reactive protein; GBS, Group B Streptococcus; PPRM, preterm prelabor membrane rupture.

Table 5. Sensitivity and exploratory association analyses

Results	Analysis	Crude incidence rate	Adjusted estimate	95% confidence interval	P-value
Clinical composite outcome associated with maternal infection	Increase in 24-hour latency	—	aOR 1.53	1.10–2.16	0.012
Suspected neonatal infection/completion of antibiotic regimen	Increase in 24-hour latency	—	aOR 1.47	1.08–2.03	0.015
Neonatal respiratory compound termination	Increase in 24-hour latency	—	aOR 0.89	0.65–1.20	0.443
Clinical composite outcome associated with maternal infection	Latency ≥ 72 hours vs < 72 hours	13/49 (26.5%) vs 15/169 (8.9%)	aOR 3.67	1.32–10.81	0.012
Suspected neonatal infection/antibiotic regimen completion	Latent period ≥ 72 hours vs < 72 hours	13/49 (26.5%) vs 19/169 (11.2%)	aOR 3.10	1.16–8.56	0.024
Neonatal respiratory composite outcome	Latency ≥ 72 hours vs < 72 hours	8/49 (16.3%) vs 45/169 (26.6%)	aOR 0.84	0.31–2.10	0.712
Clinical composite outcome associated with maternal infection	> 48 hours vs. < 24 hours; adjusted for management variables	—	aOR 7.95	1.88–39.89	0.004
Suspected neonatal infection/antibiotic regimen completion	> 48 hours vs. < 24 hours; adjusted for management variables	—	aOR 1.93	0.77–4.91	0.160
Neonatal respiratory composite outcome	> 48 hours vs. < 24 hours; adjusted for management variables	—	aOR 0.46	0.19–1.05	0.067

Primary covariate sets were used in the continuous and ≥ 72 -hour models. The maternal model, adjusted for management variables, included gestational age at the time of PPROM, cervical dilation, CRP, GBS positivity, and antibiotic latency; the model associated with neonatal infection included gestational age at delivery, antenatal corticosteroids, antibiotic latency, GBS positivity, and cesarean delivery; the respiratory model included gestational age at delivery, antenatal corticosteroids, cesarean delivery, birth weight, and neonatal sex. Since some variables emerged after the latency period, these models are direct association analyses. No multiple-test correction was applied in the secondary analyses. Abbreviations: aOR, adjusted odds ratio; GBS, Group B Streptococcus.