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## OBSTETRICS

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# Maternal Factors Associated with Early Onset Neonatal Sepsis in Preterm newborns at Maharat Nakhon Ratchasima Hospital

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### ABSTRACT

**Objective:** To investigate maternal factors associated with early-onset neonatal sepsis in preterm infants at Maharat Nakhon Ratchasima Hospital.

**Materials and Methods:** This retrospective case-control study included singleton preterm neonates born at Maharat Nakhon Ratchasima Hospital between gestational ages of 24–36<sup>+6</sup> weeks, from 2021 to 2023, totaling 497 cases. The study population consisted of 166 preterm neonates diagnosed with early-onset neonatal sepsis (EONS) and 331 preterm neonates without sepsis (case-control ratio 1:2). Maternal demographic and clinical data were obtained from medical records. Descriptive statistics summarized baseline characteristics, while multiple logistic regression model identified maternal factors associated with EONS. Associations were reported as odds ratio (OR) with 95% confidence intervals (CI), with  $p < 0.05$  considered statistically significant.

**Results:** Maternal factors significantly associated with EONS included gestational age less than 34 weeks (OR 2.77, 95%CI 1.74–4.40,  $p < 0.001$ ), chorioamnionitis (OR 3.33, 95%CI 1.21–9.17,  $p = 0.02$ ), maternal white blood cell count greater than 15,000 cells/ $\mu$ L (OR 1.92, 95%CI 1.16–3.20,  $p = 0.012$ ).

**Conclusion:** Gestational age  $< 34$  weeks, maternal chorioamnionitis, and maternal leukocytosis were significant risk factors associated with EONS in preterm neonates. Awareness of these factors may help in early recognition and clinical management.

**Keywords:** preterm neonates, early-onset neonatal sepsis, risk factors, chorioamnionitis.

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## ปัจจัยของมารดาที่สัมพันธ์กับการเกิดภาวะติดเชื้อแรกเกิดในทารกคลอดก่อนกำหนดในโรงพยาบาลมหาราชนครราชสีมา

จิตาภา เอี่ยมเจริญลาภ, จูตินันท์ สมุทรไชยกิจ

### บทคัดย่อ

**วัตถุประสงค์:** เพื่อศึกษาปัจจัยของมารดาที่สัมพันธ์กับการเกิดภาวะติดเชื้อแรกเกิดในทารกคลอดก่อนกำหนดในโรงพยาบาลมหาราชนครราชสีมา

**วัสดุและวิธีการ:** การศึกษาแบบวิเคราะห์แบบย้อนหลัง (Retrospective case-control study) ทำการศึกษาในทารกครรภ์เดี่ยวคลอดก่อนกำหนด เกิดในโรงพยาบาลมหาราชนครราชสีมา อายุครรภ์ระหว่าง 24–36<sup>+</sup><sub>6</sub> สัปดาห์ จำนวน 497 ราย ที่เกิดในช่วงปี พ.ศ. 2564 ถึงปี พ.ศ. 2566 โดยกลุ่มประชากร ได้แก่ ทารกคลอดก่อนกำหนดที่มีภาวะการติดเชื้อแรกเกิดจำนวน 166 คน และ ทารกคลอดก่อนกำหนดที่ไม่มีภาวะติดเชื้อแรกเกิดจำนวน 331 คน (อัตราส่วน 1 ต่อ 2) ข้อมูลประชากรและข้อมูลทางคลินิกของมารดาได้จากเวชระเบียน โดยใช้สถิติเชิงพรรณนาเพื่อสรุปลักษณะพื้นฐานของกลุ่มตัวอย่าง และใช้การวิเคราะห์ถดถอยโลจิสติกแบบพหุเพื่อศึกษาปัจจัยของมารดาที่สัมพันธ์กับภาวะติดเชื้อในทารกแรกเกิดในทารกคลอดก่อนกำหนด รายงานค่า odds ratio (OR) และ 95% confidence interval (CI) โดย p value < 0.05 ถือว่ามีนัยสำคัญทางสถิติ

**ผลการศึกษา:** ปัจจัยที่สัมพันธ์กับการเกิดภาวะติดเชื้อแรกเกิด อย่างมีนัยสำคัญทางสถิติ ได้แก่ อายุครรภ์ที่น้อยกว่า 34 สัปดาห์ (OR 2.77, 95%CI 1.74-4.40, p < 0.001) ภาวะการติดเชื้อในถุงน้ำคร่ำ (OR 3.33, 95%CI 1.21-9.17, p = 0.02) และระดับเม็ดเลือดขาวของมารดาที่มากกว่า 15,000 เซลล์/ไมโครลิตร (OR 1.92, 95%CI 1.16-3.20, p = 0.012)

**สรุป:** อายุครรภ์ที่น้อยกว่า 34 สัปดาห์, ภาวะติดเชื้อในถุงน้ำคร่ำ, และระดับเม็ดเลือดขาวของมารดาที่มากกว่า 15,000 เซลล์/ไมโครลิตรสัมพันธ์กับการเกิดภาวะติดเชื้อแรกเกิดของทารกคลอดก่อนกำหนด การตระหนักถึงปัจจัยเหล่านี้จะช่วยในการวินิจฉัยภาวะติดเชื้อแรกเกิดได้ตั้งแต่ระยะเริ่มต้นและให้การดูแลรักษาที่เหมาะสมในทารกคลอดก่อนกำหนด

**คำสำคัญ:** ทารกคลอดก่อนกำหนด, ภาวะการติดเชื้อแรกเกิด, ปัจจัยเสี่ยง, ภาวะการติดเชื้อในถุงน้ำคร่ำ

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## Introduction

Preterm birth is a common health problem and is the major cause of neonatal morbidity and disability. One of the primary contributors to mortality among preterm neonates is early-onset neonatal sepsis (EONS). According to the World Health Organization (WHO), approximately 13.4 million babies were born prematurely in 2020, accounting for 9.9% of all live births, or about 1 in every 10 births. In 2021, nearly one million preterm infants died before the age of five due to complications related to prematurity.<sup>(1)</sup>

In Thailand, data from the Ministry of Public Health in 2023 reported a preterm birth rate of 10.4%. According to the previous study, the incidence of preterm birth in Northeast Thailand was 10.83%.<sup>(2)</sup> In Nakhon Ratchasima province, the rate was 8.96%, while at Maharat Nakhon Ratchasima Hospital, the rate was as high as 11.96%, which is higher than the average due to referrals from surrounding hospitals. Over the period of 2000-2013 in 194 countries, the leading causes of neonatal death in the early neonatal period (age 0-6 days) were prematurity (40%), intrapartum complication (27%), and neonatal infections (8%).<sup>(3)</sup> Preterm birth affects mothers of all ages. A study conducted at Charoenkrung Pracharak Hospital found that teenage pregnancies have a notably higher rate of preterm delivery, especially in young adolescents.<sup>(4)</sup>

Early onset neonatal sepsis (EONS) is defined as a bloodstream infection occurring within the first 72 hours after birth, which is common and is a leading cause of death in neonates. As reported by a 2020 systematic review published in *Global Child Health*, the incidence of EONS between 2009 and 2018 was 3,112 cases per 100,000 live births, increasing to over 10,000 cases per 100,000 live births among preterm neonates.<sup>(5)</sup> The pathogenesis of preterm EONS is primarily associated with intra-amniotic infection, which typically begins prior to the onset of labor and contributes to preterm labor or premature rupture of membranes (PROM). Microbial-induced maternal inflammation may trigger the initiation of parturition and provoke fetal inflammatory responses,

ultimately leading to neonatal sepsis.<sup>(6)</sup>

Multiple maternal factors have been identified as potential contributors to EONS, including advanced maternal age (> 35 years), gestational age < 34 weeks, obesity, excessive gestational weight gain, preterm premature rupture of membranes (PPROM), intrapartum fever, chorioamnionitis, maternal leukocytosis (> 15,000 cells/ $\mu$ L), and elevated neutrophil-to-lymphocyte ratio (NLR) > 5.<sup>(7-12)</sup> However, the independent effects of these factors remain inconsistent across populations, particularly in our country.

Preterm birth is high risk for EONS and is associated with high mortality rates. Given the higher-than-average preterm birth rates at our institution and the clinical burden of EONS among these vulnerable neonates, identifying maternal predictors is essential for improving early detection and targeted interventions. Therefore, this study aimed to investigate maternal factors associated with EONS in preterm infants (within 72 hours after birth) at Maharat Nakhon Ratchasima Hospital, a tertiary referral center in northeastern Thailand. The findings of this study could provide useful statistical data to enhance screening and risk-based clinical care for mothers at risk for preterm birth.

## Material and Methods

This retrospective case-control study was conducted after approval from the Human Research Ethics Committee of Maharat Nakhon Ratchasima Hospital (MNRH IRB) and issued certificate number 126/2024. This study aimed to identify maternal factors associated with EONS in preterm neonates. The study was conducted on 497 preterm neonates who were born from January 2021 to December 2023 at Maharat Nakhon Ratchasima Hospital.

Eligible participants were singleton preterm neonates born at 24–36<sup>+6</sup> weeks' gestation. Neonates with incomplete medical records, congenital anomalies, or indicated preterm births were excluded. The diagnosis of EONS, as defined by the American Academy of Pediatrics, requires a positive blood or

cerebrospinal fluid culture and/or clinical signs consistent with sepsis, supported by abnormal laboratory findings. Clinical signs may include (1) abnormal body temperature ( $> 37.5^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ ), (2) heart rate abnormalities ( $< 100$  or  $> 180$  beats per minute) or delayed capillary refill ( $> 3$  seconds) or hypotension below age-specific thresholds, (3) respiratory rate  $> 60$  breaths/min, or signs of respiratory distress such as grunting, chest retractions, or  $\text{PaO}_2 < 70$  mmHg, (4) circulatory abnormalities (e.g., altered consciousness, oliguria, or venous blood pH  $< 7.25$ ), (5) gastrointestinal symptoms (e.g., poor feeding, feeding intolerance, or abdominal distension), and (6) general symptoms such as irritability, lethargy, or hypotonia.<sup>(13)</sup> Laboratory criteria supporting the diagnosis include an (1) immature-to-total neutrophil (I/T) ratio  $\geq 0.2$  or neutropenia, (2) platelet count  $< 150,000$  cells/mm<sup>3</sup>, and (3) C-reactive protein (CRP)  $> 5$  mg/L after 6 hours of life.<sup>(14)</sup>

A pilot study of 50 cases informed the planning of this study. For clarity and clinical relevance, gestational age at delivery  $< 34$  weeks, which has been consistently associated with an increased risk of EONS,<sup>(8)</sup> was selected as the main factor for the sample size justification in this study with proportions of 0.417 in cases ( $P_1$ ) and 0.579 in controls ( $P_2$ ). Assuming  $\alpha = 0.05$ , power = 0.80, a 2:1 control-to-case ratio, and adjustment for other explanatory variables ( $R^2 \approx 0.24$ ), the minimum required sample size was 164 cases and 327 controls (total = 491 neonates). For analysis, two controls per case were randomly selected from the study population during the same period (unmatched 1: 2 design) using computer-generated random numbers independent of exposure. The final dataset comprised 166 cases and 331 controls (total = 497 neonates).

Maternal demographic, obstetric, and clinical data, including antepartum, intrapartum, mode of delivery, treatment, laboratory (latest laboratory results within 72 hours prior to delivery) and neonatal outcomes, were extracted from medical records.

Descriptive statistics (mean, standard deviation, median, interquartile range, and percentage)

summarized baseline characteristics. Multiple logistic regression was used to assess maternal factors associated with EONS. Variables included in the multivariable model were maternal age, excessive gestational weight gain, PPRM, gestational age  $< 34$  weeks, chorioamnionitis, maternal  $\text{NLR} \geq 5$ , and maternal white blood cell count (WBC)  $> 15,000/\mu\text{L}$ . Selection was based on clinical relevance and prior evidence. A full-model strategy was applied, retaining all variables of theoretical or clinical importance regardless of statistical significance. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs), and  $p$  values  $< 0.05$  were considered statistically significant.

## Results

A total of 497 preterm neonates at Maharat Nakhon Ratchasima Hospital were included in this study, which comprised 166 cases with EONS and 331 cases without EONS. Maternal characteristics and pregnancy outcomes are shown in Table 1. For maternal factors, statistically significant differences were observed between the two groups, including PPRM (46.4% vs 53.8%,  $p = 0.001$ ), maternal fever (10.8% vs 4.8%,  $p = 0.022$ ), chorioamnionitis (9.0% vs 1.8%,  $p < 0.001$ ), antenatal dexamethasone used (61.4% vs 42.9%,  $p = 0.002$ ), and maternal diabetes (15.6% vs 9.6%,  $p = 0.049$ ).

EONS neonates were more frequently born before 34 weeks' gestation (58.4% vs 32.6%,  $p < 0.001$ ) and had a higher rate of very low birth weight ( $< 1,500$  g) (19.9% vs 9.7%,  $p = 0.001$ ), while non-EONS neonates more often weighed 2,500–4,000 g (33.5% vs 22.3%). Low Apgar scores ( $< 7$ ) were more common in the EONS group at both 1 minute (25.3% vs 10.3%) and 5 minutes (12.1% vs 2.7%) ( $p < 0.001$  for both). Furthermore, Neonatal intensive care unit admissions were also significantly higher among the EONS group (30.7% vs 9.4%,  $p < 0.001$ ).

Mothers of neonates with EONS exhibited significantly higher WBC counts compared to mothers of non-EONS neonates (mean  $13,749 \pm 5,087$  vs  $12,366 \pm 3,718$  cells/ $\mu\text{L}$ ,  $p = 0.001$ ). Additionally, the

NLR was significantly elevated in the EONS group [median 6.6 (IQR 3.6–10.5) vs 5.2 (IQR 3.6–7.9),  $p = 0.022$ ]. The lymphocyte percentage was lower in the EONS group ( $13.9\% \pm 7.3$  vs  $15.2\% \pm 6.4$ ,  $p = 0.034$ ).

No significant differences were observed between groups in other hematologic parameters, including hemoglobin, hematocrit, and platelet counts (Table 2).

**Table 1.** Maternal characteristics and pregnancy outcomes between two groups.

Characteristics	Early onset neonatal sepsis, n = 166	Non-early onset neonatal sepsis, n = 331	p value
Maternal age (years), mean $\pm$ SD	28.0 $\pm$ 6.92	27.1 $\pm$ 6.73	0.347
Antenatal care visit			0.254
< 8 times	87 (52.4)	155 (46.8)	
$\geq$ 8 times	79 (47.6)	176 (53.2)	
Maternal BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	23.8 $\pm$ 6.13	22.7 $\pm$ 5.29	0.328
Excessive gestational weight gain	137 (82.5)	267 (80.7)	0.715
Nulliparous	74 (44.6)	172 (52.0)	0.129
PPROM			0.001*
No PPRM	89 (53.6)	153 (46.2)	
$\leq$ 18 hours	34 (20.5)	118 (35.7)	
> 18 hours	43 (25.9)	60 (18.1)	
Maternal fever	18 (10.8)	16 (4.8)	0.022*
Maternal UTI	14 (8.4)	20 (6.0)	0.348
Chorioamnionitis	15 (9.0)	6 (1.8)	< 0.001*
Antenatal dexamethasone used	102 (61.4)	142 (42.9)	0.002*
Antenatal antibiotics used	135 (81.3)	256 (77.3)	0.353
Route of delivery			0.490
Vaginal route	94 (56.6)	187 (56.5)	
Cesarean section	72 (43.4)	144 (43.5)	
Maternal Diabetes			0.049*
Overt DM	5 (3.0)	5 (1.5)	
GDMA1	10 (6.0)	20 (6.0)	
GDMA2	11 (6.6)	7 (2.1)	
Gestational age at delivery			< 0.001*
< 34 weeks	97 (58.4)	108 (32.6)	
34-36 <sup>+</sup> 6 weeks	69 (41.6)	223 (67.4)	
Birth weight (grams), mean $\pm$ SD	1,999.2 $\pm$ 669.81	2,248.2 $\pm$ 579.34	0.001*
Birth weight			0.001*
Less than 1500 g	33 (19.9)	32 (9.7)	
1,500 – 2,499 g	96 (57.8)	188 (56.8)	
2,500 – 4,000g	37 (22.3)	111 (33.5)	
Apgar score < 7			
At 1 min	42 (25.3)	34 (10.3)	< 0.001*
At 5 min	20 (12.1)	9 (2.7)	< 0.001*
Gender			0.632
Male	96 (57.8)	183 (55.3)	
Female	70 (42.2)	148 (44.7)	
NICU admission	51 (30.7)	31 (9.4)	< 0.001*

BMI: body mass index, SD: standard deviation, n: number of patients, PPRM: preterm premature rupture of membranes, UTI: urinary tract infection, GDM: gestational diabetes, NICU: neonatal intensive care unit  
Data are expressed by n (%), mean  $\pm$  SD.

**Table 2.** Comparison of maternal laboratory results between the two groups.

Characteristics	Early onset neonatal sepsis, n = 166	Non-early onset neonatal sepsis, n = 331	p value
Hemoglobin (g/dL), mean ± SD	11.5 ± 1.36	11.6 ± 1.20	0.453
Hematocrit (%), mean ± SD	35.2 ± 4.08	35.6 ± 3.53	0.277
White blood cell (cells/μL), mean ± SD	13,749.0 ± 5,086.77	12,365.5 ± 3,718.49	0.001*
Neutrophil (%)	79.5 ± 9.61	77.9 ± 8.59	0.055
Lymphocyte (%)	13.9 ± 7.27	15.2 ± 6.39	0.034*
NLR, median (IQR)	6.6 (3.6, 10.5)	5.2 (3.6, 7.9)	0.022*
Platelet (cells/μL), mean ± SD	261,283.1 ± 72,844.53	251,121.8 ± 62,167.87	0.106

SD: standard variation, g/dL: gram/deciliter, IQR: interquartile range, NLR: neutrophil to lymphocyte ratio, n: number of patients

Data is expressed as mean ± SD, median IQR

In multivariable logistic regression, three maternal factors were independently associated with EONS. Gestational age < 34 weeks was linked to a nearly threefold increased risk (adjusted odds ratio (aOR) 2.77, 95%CI 1.74–4.40,  $p < 0.001$ ). Chorioamnionitis was also a strong predictor (aOR

3.33, 95%CI 1.21–9.17,  $p = 0.020$ ), as was maternal leukocytosis (WBC >15,000/μL; aOR 1.92, 95%CI 1.16–3.20,  $p = 0.012$ ). Other factors, including maternal age, excessive gestational weight gain, PPROM, and NLR > 5, were not significantly associated after adjustment (Table 3).

**Table 3.** Maternal factors associated with EONS.

Variables	OR (95%CI)	Adjusted OR (95%CI)	p value
Maternal Age (years)			
< 20	0.91 (0.53, 1.57)	0.71 (0.40, 1.26)	0.241
20-34	1	Ref.	
≥ 35	1.45 (0.84, 2.51)	1.39 (0.78, 2.47)	0.263
Excessive weight gain	0.88 (0.54, 1.43)	1.08 (0.65, 1.80)	0.772
PPROM	0.74 (0.51, 1.08)	0.92 (0.71, 1.18)	0.491
Gestational age at delivery < 34 weeks	2.90 (1.98, 4.27)	2.77 (1.74, 4.40)	< 0.001*
Chorioamnionitis	5.38 (2.05, 14.14)	3.33 (1.21, 9.17)	0.020*
Maternal NLR ≥ 5	1.28 (0.88, 1.87)	0.62 (0.38, 1.01)	0.054
Maternal WBC > 15,000 cells/μL	2.11 (1.38, 3.22)	1.92 (1.16, 3.20)	0.012*

PPROM: preterm premature rupture of membranes, OR: odds ratio, CI: confidence interval, NLR: neutrophil-to-lymphocyte ratio, WBC: white blood cell

## Discussion

This study found that a maternal factor associated with EONS in preterm neonates was a gestational age of less than 34 weeks, which was significantly associated with EONS (adjusted OR 2.7, 95%CI 1.74–4.40,  $p < 0.001$ ). This variable was also used for sample size estimation, and the observed association supports the initial hypothesis. This finding was consistent with the study by Chayawongrungrung et al<sup>(8)</sup>, which also reported an

association between a gestational age below 34 weeks and EONS in preterm infants. Similarly, the study by Al-Wassia et al<sup>(7)</sup> found that the lower the gestational age, the higher the risk of developing EONS. This supports the hypothesis that immature immune systems in preterm neonates contribute to an increased susceptibility to infection<sup>(15, 16)</sup>. Furthermore, preterm neonates born before 34 weeks are more likely to undergo invasive procedures, such as central venous catheterization and endotracheal



intubation, and have prolonged hospital stays, all of which increase the risk of developing EONS<sup>(17)</sup>.

Chorioamnionitis was significantly associated with the occurrence of EONS, with an adjusted OR of 3.33 (95%CI 1.21–9.17,  $p = 0.02$ ). This finding was consistent with studies by Guo et al<sup>(18)</sup>, Joachim et al<sup>(11)</sup>, and Lee et al<sup>(19)</sup>. The increased risk of EONS associated with chorioamnionitis is explained by intrauterine inflammation caused by bacterial infection ascending from the lower genital tract into the uterine cavity. The infection can invade the amniotic sac, fetal membranes, and placenta, resulting in inflammation and infection of the fetus before, during, or after delivery. Moreover, the inflammatory process triggers the release of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, which can induce preterm labor and increase neonatal susceptibility to infection<sup>(17, 20, 21)</sup>.

Maternal WBC > 15,000 cells/ $\mu$ L was also significantly associated with EONS with an adjusted OR of 1.92 (95%CI 1.16-3.20,  $p = 0.012$ ). This finding was consistent with physiological mechanisms indicating that elevated maternal WBC counts may result from the body's response to infection in the reproductive tract or intrauterine inflammation, which aligns with a diagnosis of chorioamnionitis<sup>(20, 21)</sup>. In clinical practice, maternal WBC levels are often used as part of the diagnostic criteria and management of suspected intraamniotic infection, a condition also associated with EONS in this study.

This study aimed to identify maternal factors associated with EONS in preterm neonates and was conducted at a tertiary care hospital, which may limit the generalizability of the findings to broader populations. Therefore, the study population may differ from those in primary or secondary care settings. Additionally, demographic characteristics and access to maternal care in this region may not reflect those in other provinces or countries. Nevertheless, the large sample size and comprehensive collection of maternal clinical data enhance the study's internal validity. These findings may still be applicable to similar tertiary hospitals with

comparable referral patterns and maternal risk profiles.

The findings offer valuable insights that may support early clinical decision-making, guide clinical management, and increase awareness among obstetricians and pediatricians. This study had several limitations. The retrospective design, reliance on incomplete medical record data, and single center setting, may have led to missing information for certain variables or maternal clinical symptoms. Future prospective studies can overcome these limitations and strengthen the evidence.

## Conclusion

This study identified several maternal factors associated with an increased risk of EONS, including chorioamnionitis, gestational age less than 34 weeks, and maternal leukocytosis. This integration offers a promising approach to improving early recognition and perinatal care of mothers and preterm neonates at risk of EONS.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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