Incidence and Risk Factors of Neonatal Sepsis in Preterm Premature Rupture of Membranes before 34 Weeks of Gestation

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ABSTRACT

Objective: Early-onset neonatal sepsis (EONS) is a leading cause of newborn morbidity and mortality, particularly in preterm premature rupture of membranes (PPROM) before 34 weeks of gestation, in which expectant management was performed until reaching 34 weeks of gestation, evidence of maternal chorioamnionitis, or unfavorable fetal conditions. The interval between membrane rupture and delivery has a positive correlation with neonatal sepsis. The purpose of this study was to investigate the incidence and risk factors of EONS in PPROM.

Materials and Methods: This was a retrospective cross-sectional study. The medical records of pregnant women who gave birth between 2005 and 2018 and their newborns were reviewed. The inclusion criterion was singleton pregnancies complicated by PPROM between 24 and 33^{+6} weeks of gestation. Multifetal pregnancies, fetal malformation, stillbirths, and records with incomplete data were excluded. PPROM was diagnosed by obstetricians while EONS was diagnosed by neonatologist.

Results: The incidence of EONS in with PPROM was 24%. Risk factors included excessive maternal weight gain based on IOM (OR = 2.40, 95% CI = 1.16-4.94), extremely preterm at admission (before 28 weeks of gestation) (OR = 3.38, 95% CI 1.12-10.21) and very low birth weight (≤ 1,500 g) (OR 3.68, 95% CI = 1.86-7.30). Maternal hematologic laboratory results were not associated with neonatal sepsis.

Conclusion: The incidence of EONS in PPROM was similar to data provided by other studies. Obstetricians and pediatricians should be cautious about neonatal sepsis, especially in cases of excessive maternal weight gain, extremely preterm admissions, and very low birth weight.

Keywords: Early-onset neonatal sepsis; incidence; PPROM; risk factors (Siriraj Med J 2022; 74: 169-177)

INTRODUCTION

Preterm birth is defined as babies born prior to completion of 37 weeks of gestation. At Siriraj Hospital, the incidence of preterm birth between 28 and 37 weeks of gestation is 9-13%.[1,2] Due to the immature development of several organs, these babies tend to have short-term or long-term morbidities in the respiratory system (respiratory distress syndrome, bronchopulmonary dysplasia, apnea of prematurity), gastrointestinal system (feeding intolerance, necrotizing enterocolitis, growth failure), immunological system (infection) and central nervous system (intraventricular hemorrhage, cerebral palsy, neurodevelopmental delay, hearing loss, retinopathy of prematurity).[3]

One of the causes of preterm birth is preterm premature rupture of membranes (PPROM) in which the fetal

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Received 25 October 2021 Revised 15 January 2022 Accepted 21 January 2022
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http://dx.doi.org/10.33192/Smj.2022.21

membranes spontaneously rupture before completion of 37 weeks of gestation and onset of labor. At Siriraj Hospital, the incidence of PPROM between 24 and 37 weeks of gestation is 2.93%.[4] After the rupture of fetal membranes, microorganisms from the maternal lower genital tract ascend the uterine cavity, resulting in infectious morbidities such as chorioamnionitis, fetal inflammation and neonatal sepsis. Besides PPROM, risk factors of neonatal sepsis include preterm labor, low birth weight, maternal colonization of group B *streptococcus*, chorioamnionitis and intrapartum infection.[5,6] The interval between the rupture of membranes and delivery has a positive correlation with neonatal sepsis.[7] Early-onset neonatal sepsis (EONS) is an important cause of morbidity and mortality of newborns. Short-term outcomes are hypotension requiring vasopressor support; respiratory distress or suppression requiring intubation or noninvasive ventilation; and hyper- and hypoglycemia, thrombocytopenia, and disseminated intravascular coagulation (DIC). Long-term outcomes are bronchopulmonary dysplasia (BPD), brain injury, including periventricular leukomalacia (PVL), neurodevelopmental delays, and cerebral palsy.[8]

Management of PPROM remains challenging as it is difficult to balance the risk of terminating a pregnancy as long as expectant management exists. While expectant management poses a risk of maternal and fetal infection, placental abruption, and umbilical cord accidents, termination of pregnancy, especially at an early gestational age, presents a danger of prematurity.[9] Over the last few decades, the decision to terminate a pregnancy with PPROM complications have been based on evidence of maternal chorioamnionitis or unfavorable fetal conditions. Chorioamnionitis is defined by maternal fever and uterine tenderness, which results in severe infection in newborn babies. Indications of early stage chorioamnionitis have been proposed, however, they remain controversial and unreliable. Our aim was to study the incidence of EONS and parameters associated with this condition.

MATERIALS AND METHODS

Study design

This was a retrospective cross-sectional study approved by the institutional ethical committee.

Participants

Based on previous report from Arora and colleagues[10], the sample size of 274 samples would yield a power of 80% and type I error of 5%, 2-sided. The medical records of pregnant women who gave birth between 2005 and 2018 were reviewed. The inclusion criterion was singleton pregnancies affected by PPROM between 24 and 33^{+6} weeks of gestation. Multifetal pregnancies, fetal malformation, stillbirths, indicated preterm birth conditions such as maternal diseases, preeclampsia and placenta previa, and records with incomplete data were excluded. Gestational age was defined by menstrual history or ultrasonography performed before 20 weeks of gestation.

Outcomes

The clinical parameters included maternal demographic data, parity, history of previous preterm birth, body mass index (BMI), weight gain during pregnancy according to the Institute of Medicine (IOM) pregnant women, diabetes mellitus status, gestational age at PPROM and at delivery, interval between rupture of membranes and delivery, dexamethasone dosage, delivery mode, birth weight of newborns, APGAR score, diagnosis of EONS, length of neonatal hospital stay, and neonatal discharge status. The maternal hematological parameters included complete blood count (CBC), neutrophils to lymphocytes (N/L) ratio, and erythrocyte sedimentation rate (ESR). The IOM recommended that pregnant women should have a total weight gain of 12.5 to 18 kg, 11.5 to 16 kg, 7 to 11.5 kg, and 5 to 9 kg for those whose pre-pregnancy BMI were categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (≥30 kg/m^2), respectively.[11,12]

All newborns were assessed by neonatologist at Siriraj Hospital. The EONS was defined by a positive culture of pathogenic bacteria in the blood or cerebrospinal fluid (CSF) within 72 hours after birth. Blood culture remains the diagnostic standard for EONS. CSF culture should ideally be performed along with blood culture for newborns who are at the highest risk for EOS. However, lumbar puncture should not be performed if the newborn's clinical condition was compromised, or antibiotic initiation would be delayed by the procedure.[13]

In our institute, all PPROM cases of less than 34 weeks of gestation were managed by a combined administration of antibiotics (ampicillin/amoxicillin plus erythromycin)[14], corticosteroids, and short-term tocolytics to complete course of corticosteroids. After completing the course of antibiotics and corticosteroids, expectant management was performed until 34 weeks of gestation when delivery was induced. Termination of each pregnancy was individually encouraged before 34 weeks using evidence of maternal chorioamnionitis or unfavorable fetal conditions. Complete blood count and ESR were checked every other day from admission until delivery.

Statistical analysis

The continuous variables are presented as mean ± SD, median, and range. The categorical variables are presented as frequencies and percentage. A T-test was used to compare two groups of continuous data which were normally distributed while the Mann-Whitney U test was used to compare differences between two independent groups when the dependent variables were either ordinal or continuous, but not normally distributed. The Chi-square test was used to compare a group with a value or to compare two or more groups, always using categorical data. Risk factors of EONS were shown as an odds ratio by binary logistic regression analysis. IBM SPSS Statistics version 21 (Copyright International Business Machines Corporation and other(s) 1989, 2012) was used for statistical analysis. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

A total number of 407 medical records were initially included into this study. One hundred and thirty-three records were excluded. Data from the remaining 274 records were used for further analysis (Fig 1).

The overall incidence of EONS in PPROM before 34 weeks of gestation was 24%. The trend of incidence has decreased over the past 14 years (Fig 2). The maternal characteristics and pregnancy outcomes were shown in Table 1. Maternal age was not significantly different between those with and without EONS, which was similar to parity and history of previous preterm birth. The PPROM interval prior to delivery, clinical chorioamnionitis and unfavorable fetal conditions did not relate to neonatal sepsis. Most pregnant women received four doses of dexamethasone before delivery. There was only one case of prolapsed cord among those without EONS. Placental abruption was not found in both groups.

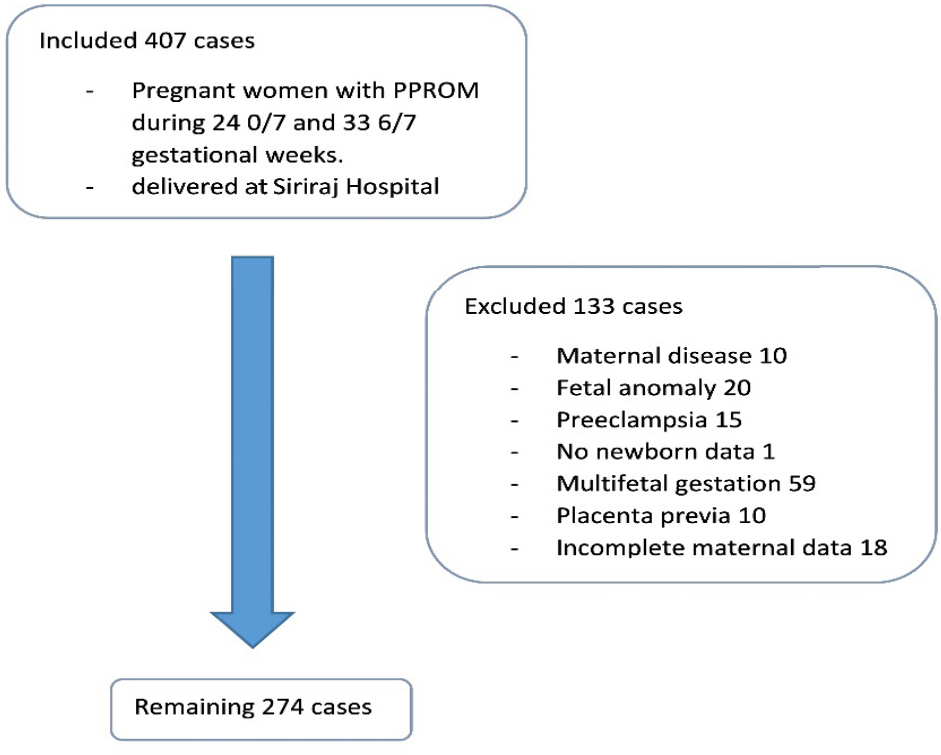

Fig 1. Flow of PPROM cases in Siriraj Hospital from 2005 to 2018

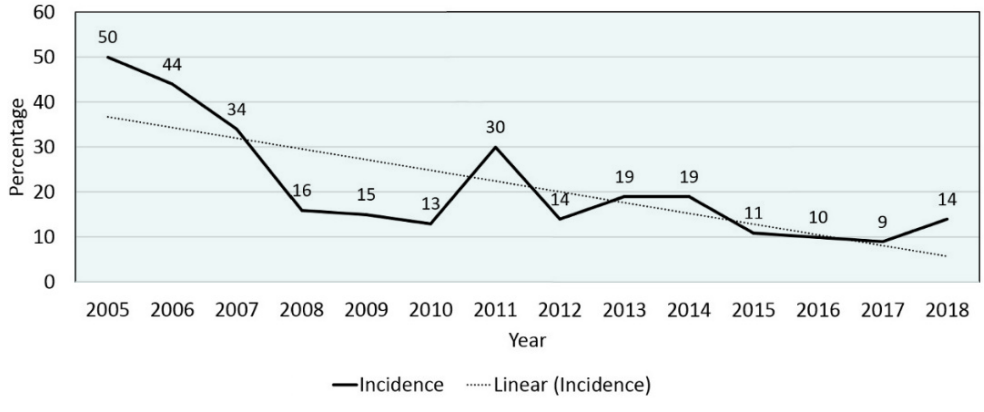

Fig 2. Incidence of EONS in PPROM pregnancies before 34 weeks of gestation at Siriraj Hospital from 2005 to 2018.

TABLE 1. Maternal characteristics and pregnancy outcomes of 274 women enrolled in the study in the PPROM without EONS or PPROM with EONS group.

Variables	PPROM without EONS (n=221)	PPROM with EONS (n=53)	*P*
Maternal age (years)	27.9 ± 7.2	28.8 ± 6.5	0.386*
<20	37 (16.7%)	5 (9.4%)	0.381#
20-34	139 (62.9%)	38 (71.7%)	
≥35	45 (20.4%)	10 (18.9%)	
Parity			
Nulliparous	125 (56.6%)	37 (69.8%)	0.088#
Multiparous	96 (43.4%)	16 (30.2%)	
Previous PTB history	23 (10.4%)	1 (1.9%)	0.056##
Weight gain (kg)	9.8 ± 4.7	11.7 ± 5.0	0.021*
Non-excessive	161 (81.7%)	28 (65.1%)	0.016#
Excessive	36 (18.3%)	15 (34.9%)	
GA at admission (weeks)	32 (25 - 34)	31 (25 - 34)	0.007†
$24\text{-}27^{+6}$	8 (3.6%)	6 (11.3%)	0.027#
$28\text{-}31^{+6}$	60 (27.1%)	18 (34.0%)	
$32\text{-}33^{+6}$	153 (69.2%)	29 (54.7%)	
GA at delivery (weeks)	33 (25 - 34)	32 (26 - 34)	0.003†
$24\text{-}27^{+6}$	8 (3.6%)	6 (11.3%)	0.150
$28\text{-}31^{+6}$	50 (22.6%)	13 (24.5%)	
$32\text{-}33^{+6}$	163 (73.8%)	34 (64.2%)	
PPROM interval prior to delivery (hr)	26 (0 - 523)	25 (0 - 241)	0.279†
<18	99 (44.8%)	25 (47.2%)	0.353#
18-48	35 (15.8%)	12 (22.6%)	
>48	87 (39.4%)	16 (30.2%)	
Dexamethasone (dose)			
0	14 (6.3%)	6 (11.3%)	0.164#
1	80 (36.2%)	15 (28.3%)	
2	17 (7.7%)	9 (17.0%)	
3	11 (5.0%)	2 (3.8%)	
4	99 (44.8%)	21 (39.6%)	
Delivery mode			
Vaginal delivery	163 (73.8%)	40 (75.5%)	0.863#
Cesarean section	58 (26.2%)	13 (24.5%)	
Clinical chorioamnionitis	8 (3.6%)	2 (3.8%)	1.000##

TABLE 1. Maternal characteristics and pregnancy outcomes of 274 women enrolled in the study in the PPROM without EONS or PPROM with EONS group. (Continue)

Variables	PPROM without EONS (n=221)	PPROM with EONS (n=53)	*P*
Unfavorable fetal conditions	16 (7.2%)	6 (11.3%)	0.396##
Birth weight (g)	1891 ± 389	1626 ± 350	<0.001*
<1,500	29 (13.1%)	19 (35.8%)	<0.001#
1,500-2,499	179 (81.0%)	34 (64.2%)	
2,500-3,999	13 (5.9%)	0	
APGAR score at 1 min	8 (0 - 10)	8 (1-10)	0.149†
APGAR score at 5 mins	10 (0 - 10)	9 (5 - 10)	0.016†
Length of neonatal hospital stay (days)	10 (0 - 158)	30 (2 - 218)	<0.001†
<7	61 (27.6%)	1 (1.9%)	<0.001#
7-30	111 (50.2%)	26 (49.1%)	
>30	49 (22.2%)	26 (49.1%)	
Neonatal discharge status			
Alive	217 (98.2%)	52 (98.1%)	1.000#
Deceased	4 (1.8%)	1 (1.9%)	

Abbreviations: PPROM=preterm premature ruptured of membranes, EONS=Early-onset neonatal sepsis, PTB=preterm birth, GA= gestational age

* Mean ±SD, p-value (T-test)

Count, p-value (Chi-square)

Count, p-value (Fisher's exact test)

† Median, p-value (Mann-Whitney U test)

The parameters significantly associated with EONS included excessive maternal weight gain, gestational age at admission, gestational age at delivery and birth weight. An earlier gestational age at admission meant higher incidence of EONS as well as gestational age at delivery. Again, a lower birth weight meant higher chance for neonatal sepsis.

Newborns with EONS stayed in the hospital longer. The overall mortality rate of newborns from PPROM mothers is 2%. There is no statistical difference in mortality rate between the two groups.

Laboratory results were obtained from 241 women and data comparing cases with and without EONS at admission, before delivery and difference from admission to delivery are shown in Table 2. All maternal laboratory results were similar between the EONS and no EONS group.

Pregnant women in the EONS group gained more weight than the other group. According to IOM guidelines for weight gain during pregnancy, the odds ratio (OR) of EONS among pregnant women with excessive weight gain was 2.40 (95% CI 1.16-4.94). Furthermore, risk factors of EONS at admission before 28 weeks of gestation was preterm (OR = 3.38, 95%CI 1.12-10.21) and low birth weight ≤ 1,500g (OR 3.68, 95%CI = 1.86-7.30), as shown in Table 3.

TABLE 2. Maternal laboratory results in PPROM without EONS and PPROM with EONS groups

Variables	At admission			Before delivery			Difference from admission to delivery		
	No EONS (n=193)	EONS (n=48)	*P*	No EONS (n=193)	EONS (n=48)	*P*	No EONS (n=92)	EONS (n=20)	*P*
Hb (g/dl)	11.5 ± 1.3	11.3 ± 1.2	0.21*	11.2 ± 1.5	11.2 ± 1.2	0.89*	-0.6 ± 1.2	-0.1 ± 0.9	0.08*
Hct (%)	35.2 ± 3.8	34.2 ± 3.6	0.10*	34.3 ± 4.4	34.1 ± 3.6	0.73*	-1.8 ± 3.3	-0.2 ± 2.8	0.06*
WBC (10^3 cells/ul)	13.5 ± 7.3	13.3 ± 4.2	0.86*	14.5 ± 7.5	15.1 ± 4.6	0.60*	2.1 ± 5.0	4.3 ± 4.2	0.74*
N (%)	78.2 ± 7.3	76.9 ± 8.7	0.32*	80.0 ± 8.2	80.0 ± 8.7	0.99*	3.9 ± 9.8	7.4 ± 11.4	0.16*
L (%)	15.4 ± 6.0	16.3 ± 6.9	0.40*	14.1 ± 6.6	14.0 ± 6.9	0.93*	-2.7 ± 7.0	-5.4 ± 8.2	0.14*
N/L ratio	5.2 (1.1–27.4)	4.3 (1.7–21.5)	0.32†	5.6 (1.1–46.4)	6.4 (1.7–36.8)	0.99†	1.6 (-2.3–40.1)	3.0 (-8.1–34.2)	0.74†
Plt (10^3 cells/ul)	271.4 ± 62.9	272.7 ± 78.7	0.90*	268.7 ± 61.6	269.6 ± 73.3	0.93*	-5.6 ± 38.2	-7.4 ± 38.5	0.84*
ESR (mm/hr)	64.2 ± 19.5	62.2 ± 18.0	0.56*	64.2 ± 21.2	62.7 ± 18.2	0.69*	0.1 ± 18.8	7.6 ± 14.4	0.15*

Abbreviations: Hb = Hemoglobin, Hct = Hematocrit, WBC = White Blood Cells Count, N = Neutrophils, L = Lymphocytes, Plt = Platelets, ESR = Erythrocyte Sedimentation Rate

* Mean ±SD, p-value (T-test)

† Median, p-value (Mann-Whitney U test)

TABLE 3. Maternal laboratory results in PPROM without EONS and PPROM with EONS groups

Risk factors	OR	95% CI	P
Excessive weight gain	2.40	1.16 – 4.94	0.016
BMI at admission	1.04	0.96 – 1.12	0.324
Gestational age at admission			
24-27^{+6} weeks	3.38	1.12 – 10.21	0.023
28-31^{+6} weeks	1.57	0.81 – 3.04	0.177
32-33^{+6} weeks	1.00	-	-
VLBW (≤ 1,500 g)	3.68	1.86 – 7.30	<0.001

Abbreviations: BMI = body mass index, VLBW = very low birth weight

DISCUSSION

The overall incidence of EONS in pregnant women with PPROM before 34 weeks of pregnancy was found to be 24% in this study. We chose to study gestational age less than 34 weeks because PPROM that arises beyond 34 weeks of gestation is not treated expectantly, newborn sepsis is infrequent. Our incidence was in agreement with certain research[10] but not with others.[15,16] We hypothesize that the difference in incidence between hospitals is due to the varying diagnostic criteria used to identify EONS. During the 14-year period, the incidence of EONS in PPROM pregnancies before 34 weeks of gestation seems to have decreased. This could either be the result of better guideline management for premature rupture of membranes[14] or more advanced neonatal management. However, EONS incidence in preterm was higher than term deliveries. In Siriraj Hospital, the perinatal mortality rate has continuously declined and was less than 10%. The survival rate of premature babies has been increased due to the improvement of obstetric and newborn care. The well-trained neonatologists and excellent equipment result in the best care for newborns.[1]

Our study found that a maternal risk factor for EONS was excessive weight gain during pregnancy, according to IOM recommendations (OR = 2.40, 95%CI = 1.16-4.94; p=0.016). According to Stotland NE, et al., who conducted a retrospective cohort study in singleton births, the rate of neonatal infection was higher when maternal weight gain was above IOM guidelines, when compared to the appropriate or low weight gain group (5.86%, 4.44% and 3.38% respectively).[17] It was reported earlier that the incidence of sepsis among newborns of obese women was higher than those of normal-weight women.[18,19] Maternal overweight and obesity increased the risk of EOS by group B Streptococcus, Staphylococcus aureus, and Escherichia coli. Half of the association was mediated through preeclampsia, cesarean section, and preterm delivery.[19] Furthermore, obesity is a low-grade inflammatory state mediated primarily by leptin[20], which is associated with an increase in circulating inflammatory markers that are well characterized in the context of preeclampsia and maternal intrauterine infections. Since incremental weight gain has been associated with higher leptin levels[21], systemic inflammation may play a role in the higher incidence and trends of neonatal morbidities.[18]

Neonatal conditions at birth affect a baby's life in many aspects. According to previous studies[22-26], unanimous agreement states that gestational age, birth weight and APGAR scores play a vital role in neonatal well-being and complications. A study by Belachew A, et al. found that prematurity increased the risk of neonatal sepsis 3.36 times compared with term newborns (95% CI 2.50-4.54), and low birth weight (birth weight <2,500 grams) increased the risk of neonatal sepsis 1.42 times compared to the normal birth weight group (95% CI 1.07-1.88).[22] Meanwhile, Thavarajah H, et al. claimed that there was a statistically significant difference in the incidence of neonatal sepsis among different APGAR groups (low = 0-3, intermediate 4-6, normal = 7 or more).[23] Prematurity impairs adequate tissue oxygenation due to an immature respiratory function. An underdeveloped immune system along with hypoxic conditions put these babies at higher risk of infection. Our study found that a very low birth weight ≤ 1,500 g was associated with increased risk of EONS (OR 3.68, 95%CI 1.86-7.30).

Maternal hematological parameters such as white blood cell count (WBC) and erythrocyte sedimentation rate (ESR) have been proposed as predictors of chorioamnionitis and fetal infection but with some degree of controversy.[27-31] Panwar C, et al. mentioned that maternal WBC >12,000/mm^3 could predict EONS with a sensitivity of 67.2% and a specificity of 77.5% but without achieving statistical significance.[32] However, Mayuka WAB, et al. concluded that maternal WBC >12,000 /mm^3 was significantly associated with neonatal sepsis.[33] Our goal was to find parameters associated with EONS, but we did not notice any significant relationship between maternal hematological parameters and EONS. One possible explanation is that leukocytosis in PPROM mothers was the result of corticosteroids injections and not infection.[34] Many studies have advocated the usefulness of an elevated Neutrophils/Lymphocytes (N/L) ratio to predict adverse outcomes in PPROM and is associated with chorioamnionitis and EONS in preterm babies.[30,35,36] Contradicting this suggestion, the N/L ratio in our study was not significantly associated with EONS in PPROM. Future studies that can control the effect of corticosteroids might show the true relationship between leukocytosis, chorioamnionitis, and neonatal sepsis.

The strength of this study was that it found more information about maternal hematological parameters and EONS, about which there is relatively little knowledge. However, it was limited by its retrospective nature, low power in subgroup analysis and incomplete data of some parameters. More prospective studies should be carried out to eliminate these limitations.

CONCLUSION

In conclusion, the incidence of EONS in pregnant women with PPROM before 34 weeks of gestation was 24%, indicating a decrease over time. Excessive maternal weight gain, extremely preterm at admission and low birth

weight are associated with increased incidence of EONS, which affects the well-being of babies born prematurely. From this study, some maternal hematologic parameters may not reveal any risk factors of EONS. A regular check of some parameters to guide the management of PPROM cases should be considered.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Dr.Supasaek Virojanapa and Julaporn Pooliam for assistance with statistical analysis.

No conflict of interest

This study passed the requirements of the ethical committee at SIRB, COA no. Si 106/2019.

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