www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2021;10(1):e100132
doi: 10.7363/100132
Received: 2019 Aug 22; revised: 2020 Jan 26; accepted: 2020 Feb 02; published online: 2020 Dec 28

Original article

Mean platelet volume in asymptomatic chorioamnionitis-exposed infants. A retrospective case-control study

Atef Alshafei, Moustafa Hassan, Yaser El saba, Anwar Khan, Mahmoud Ahmed

Neonatology Section, Pediatric Department, Dubai Hospital, Dubai, UAE

Abstract

Introduction: Maternal chorioamnionitis (CA) is a serious condition causing several neonatal morbidities and long-term neurodevelopmental sequelae in exposed infants. Current guidelines still recommend admission, laboratory evaluation, and antibiotic administration to all CA-exposed infants. The incidence of early-onset neonatal sepsis (EOS) is currently low, owing to the routine intrapartum antibiotic administration to mothers identified to be at risk of developing CA. New diagnostic tools for early diagnosis of sepsis in apparently healthy infants exposed to maternal CA are needed. Previous studies showed that mean platelet volume (MPV) is evolving as a potential inflammatory marker of neonatal sepsis. We aimed to study whether MPV can be used as an adjuvant diagnostic tool for EOS in asymptomatic CA-exposed infants.

Objective: To evaluate the role of MPV as an adjuvant biomarker of EOS in cases of asymptomatic CA-exposed infants.

Design: Retrospective case-control study.

Setting: A tertiary care Neonatal Intensive Care Unit (NICU).

Patients: Asymptomatic CA-exposed infants 37-40 weeks of gestation admitted between May 2016 and April 2019 to the NICU of Dubai Hospital, UAE.

Results: A total of 1,300 infants were admitted to NICU during the study period. Fifty-eight infants were included in the CA-exposed group and met the inclusion criteria, and 63 infants were matched as controls. No statistically significant differences were found in the MPV between the CA-exposed infants' group and the control group. Similarly, no significant differences were noted in total white blood cell count, platelet count, and absolute neutrophil count between the two study groups. Inflammatory markers were significantly elevated in the CA-exposed group; however, blood cultures were sterile in all included infants.

Conclusions: MPV is not a sensitive marker of EOS in asymptomatic CA-exposed infants whose mothers received intrapartum antibiotic prophylaxis.

Keywords

Chorioamnionitis, mean platelet volume, sepsis, neonate.

Corresponding author

Atef Alshafei, MRCPCH, NICU, Dubai Hospital, Dubai, UAE; postal address: NICU, Pediatrics Department, Dubai Hospital, Dubai, PO Box: 7272, UAE; e-mail: ahalshafei@dha.gov.ae.

How to cite

Alshafei A, Hassan M, El saba Y, Khan A, Ahmed M. Mean platelet volume in asymptomatic chorioamnionitis-exposed infants. A retrospective case-control study. J Pediatr Neonat Individual Med. 2021;10(1):e100132. doi: 10.7363/100132.

Introduction

Chorioamnionitis (CA) – or intrauterine inflammation, infection, or both (Triple I) – refers to inflammation of the fetal membranes (chorion and amnion), mostly secondary to ascending bacterial infection through the maternal genital tract [1, 2]. CA is commonly associated with premature rupture of membranes, preterm deliveries, early-onset neonatal sepsis (EOS), and possible long-term neurodevelopmental disorders and cerebral palsy [3]. Because of these adverse neonatal outcomes, the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) guidelines for the prevention of perinatal group B streptococcal (GBS) disease, have recommended that all CA-exposed asymptomatic term infants should be admitted, evaluated, and treated with broad-spectrum antibiotics [4-6]. These guidelines were based on studies conducted before the era of widespread intrapartum antibiotics prophylaxis (IAP) implementation, in cases of suspected CA, prolonged rupture of membranes (PROM), or maternal GBS colonization. At present, the risk of culture-positive EOS in asymptomatic CA-exposed infants whose mothers received IAP is extremely low [7, 8]. Accordingly, this strategy has been called into question based on the recent data that only address close clinical monitoring of all asymptomatic term infants exposed to maternal CA [9-11]. Close clinical monitoring would potentially reduce the unnecessary administration of empiric antibiotics, mother-infant separation, health care costs, and prevent longer hospital stays. However, delayed administration of antibiotics to apparently healthy asymptomatic infants who are actually infected could have deleterious short- and long-term outcomes. Blood culture and C-reactive protein (CRP) are the tools currently used for neonatal EOS diagnosis. The sensitivity of blood cultures is reduced, and they are commonly negative in those infants with the current IAP routine use. Platelet indices, especially increased mean platelet volume (MPV), have been studied before, as a promising sensitive neonatal sepsis marker [12-15]. With the development of invasive sepsis, the production of larger and younger platelets in the peripheral circulation precedes the subsequent development of thrombocytopenia, secondary to bone marrow suppression [16]. This study aimed to evaluate MPV as a sensitive marker of EOS in CA-exposed infants in order to help determine whether these infants need to be treated or simply monitored in maternity wards.

Materials and methods

Study design, setting, and participants

We conducted a retrospective case-control study of consecutive neonates admitted to the Neonatal Intensive Care Unit (NICU) of the Dubai Hospital, UAE, between May 2016 and April 2019. Ethical approval was obtained from the Dubai Scientific Research Ethics Committee (DSREC). A total of 121 term infants were included in the study, of whom 58 were admitted to the NICU due to suspected maternal CA and were classified as cases, and 63 matched healthy term infants delivered by mothers with uneventful pregnancies were classified into the control group.

Study protocol

CA-exposed infants were asymptomatic term infants (37-40 weeks of gestation) and were admitted and received antibiotics, as per hospital protocol that follows the current AAP and CDC guidelines. Gestational age was determined by ultrasound and the first day of the last normal menstrual period. Diagnosis of suspected CA was made by the obstetrician, either before delivery or

within 4-6 hours after labor. Maternal CA diagnosis was clinically suspected in cases of intrapartum fever of 38.0°C or higher, and one of the following signs: purulent or foul-smelling uterine discharge, fundal tenderness, fetal or maternal tachycardia, or maternal leukocytosis. Full blood count (FBC) data, including platelet count, white blood cell (WBC) count, absolute neutrophil count (ANC), and MPV were collected for all included infants. In the CA-exposed infants, additional blood culture results on admission and CRP at 24 hours of age were also recorded. Three days after admission, FBC and CRP data were collected again, for comparison. The FBC was performed using an automated hematology analyzer (DxH800; Beckman Coulter, USA) with ethylenediaminetetraacetic acid (EDTA) anticoagulated whole blood samples. Blood culture was performed by a sample of 1 ml of venous blood, transferred into a BACTEC culture vial (BACTEC FX/VIRTUE BacT/ALERT). CRP was measured by an immunoturbidimetric method, using the Roche Cobas C501/502 CRP L3 clinical chemistry analyzer, according to the operator's manual for operating instructions, maintenance, and troubleshooting (Roche Diagnostics, Indianapolis, IN, USA). All infants admitted to the NICU received ampicillin and gentamicin, shortly after a full clinical and laboratory sepsis evaluation. Antibiotics were discontinued after 48 hours if the infant remained asymptomatic and blood culture and CRP were negative. However, the treatment duration would be extended to 5-7 days, if inflammatory markers were positive, despite sterile blood cultures. Maternal demographic data, mode of delivery, birth weight, gender, maternal GBS status, duration of ruptured membranes, intrapartum antibiotic administration, and Apgar scores were recorded. The medical records of all infants were examined for maternal CRP and FBC, including WBC count, ANC, platelet count, and MPV at the time of delivery. The definitions of hematologic sepsis indices in CA-exposed infants were defined as leukopenia (total WBC count ≤ 5,000/μL and ANC < 1,000) and leukocytosis (total WBC count ≥ 20,000/μL). Thrombocytopenia was defined by a platelet count <100,000/μL. The normal reference value for CRP was < 5 mg/L. Exclusion criteria included preterm infants, infants with known blood disorders or chromosome abnormalities, birth asphyxia, and symptomatic term infants on admission. Infants were considered symptomatic if any of the following criteria were observed on admission: temperature instability, apnea, poor perfusion, need for ventilation support, hypotonia, feeding intolerance, bradycardia (< 100/min), tachycardia (> 200/min), or hypotension, requiring inotropic support.

Statistical analysis

Data analysis was done using the IBM® SPSS® Statistics 23.0. The quantitative data were presented as mean and standard deviations (SD). The qualitative data were presented as count and percentages. Student's t-test was used to compare quantitative data between the two groups, while a chi-square test was used to compare the qualitative data. Paired samples t-test was used to compare the quantitative data at two different time points for the same group, and McNemar's test was used for the qualitative data. Receiver-operating characteristics (ROC) curve was used to measure the MPV validity in the diagnosis of neonatal sepsis, and the area under the curve (AUC) was calculated. P-value < 0.05 was considered statistically significant.

Results

During the study period, a total of 1,300 infants were admitted to the NICU, of whom 58 (0.4%) were healthy CA-exposed infants. There were no statistically significant differences between the study and control groups in Apgar score, gender, and maternal age ($p > 0.05$). However, gestational age and birth weight were higher in the CA-exposed group than in the control group ($p = 0.001$ and $p = 0.012$, respectively). The clinical and demographic data of the two groups are shown in **Tab. 1**. No statistically significant MPV differences were found between the two groups ($p = 0.410$) and no significant MPV change was observed in the CA-exposed infants, on admission and on day 3 ($p = 0.556$). Similarly, no significant differences were noted in total WBC count, platelet count, and ANC between the two study groups, as shown in **Tab. 2**. The AUC for MPV was 0.557 (asymptotic significance of 0.277 and standard error of 0.053; $p > 0.05$), showing no significant cut-off value; hence MPV was a statistically insignificant parameter in predicting neonatal sepsis in CA-exposed infants, as shown in **Fig. 1**. However, the platelet count was significantly higher on day 3, compared to day 1, in CA-exposed infants ($p = 0.012$). In the CA-exposed group, 3 infants (5%) who appeared asymptomatic on admission, developed signs of clinical sepsis, in the form of respiratory distress

Table 1. Demographic data of the chorioamnionitis (CA)-exposed infants' and the control group.

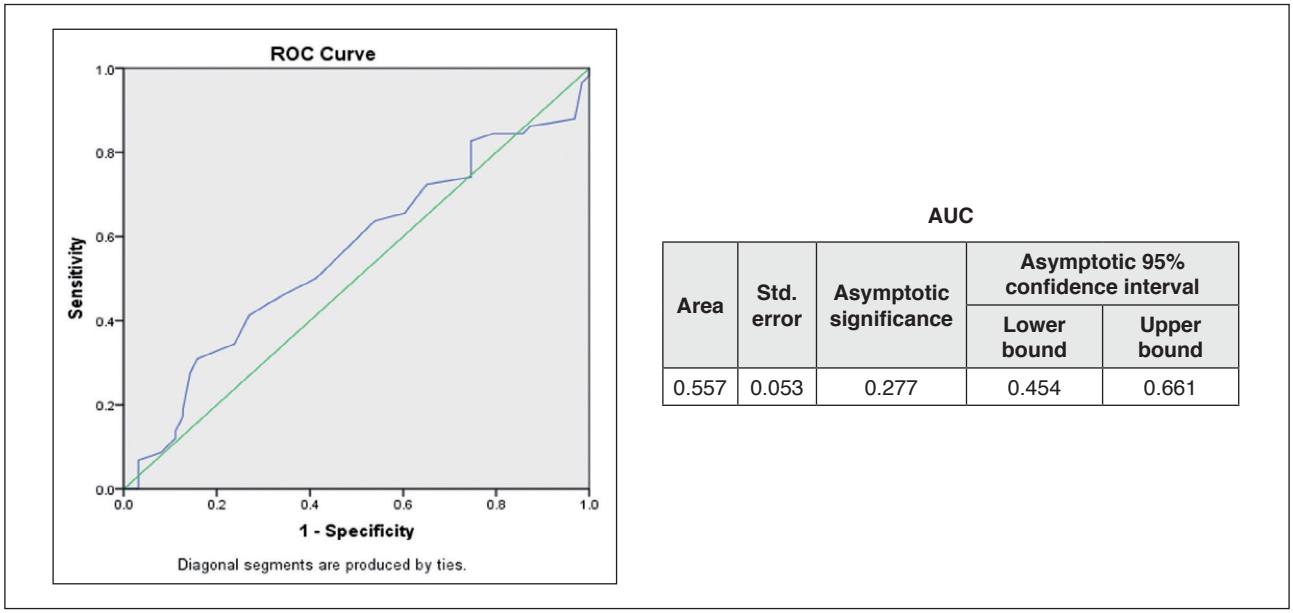
	CA-exposed infants' group (n = 58)	Control group (n = 63)	Independent t-test	
			t [a]	p-value
BW (g)	3,215.47 ± 520.00	2,979.52 ± 492.38	2.563	0.012
GA	39.22 ± 1.17	37.97 ± 1.51	5.076	0.001
Apgar score 1 minute	8.4 ± 1.31	8.70 ± 0.78	1.526	0.131
Apgar score 5 minutes	9.64 ± 0.81	9.84 ± 0.45	1.689	0.095
Maternal age	29.60 ± 4.95	31.48 ± 5.54	1.954	0.053
Male	28 (48.3%)	41 (65%)	3.479 [b]	0.062
Female	30 (51.7%)	22 (34.9%)		
NVD	27 (46%)	33 (52%)	0.429 [b]	0.521
CS	31 (54%)	30 (48%)		

CA: chorioamnionitis; BW: birth weight; GA: gestational age; NVD: normal vaginal delivery; CS: caesarean section.
$p < 0.05$: significant.
[a] Student's t-test; [b] Chi-square test.

Table 2. Full blood count (FBC) parameters of infants and mothers of the two study groups.

	CA group (n = 58)	Control group (n = 63)	Independent t-test	
			t [a]	p-value
Infants				
WBC count (× 10^3/mm^3)	14.67 ± 5.91	14.07 ± 5.33	0.586	0.559
ANC (× 10^3/mm^3)	9.32 ± 4.70	8.37 ± 4.87	1.080	0.282
Platelet count (× 10^3/mm^3)	257.60 ± 70.70	271.27 ± 64.85	1.109	0.270
MPV (fL)	8.29 ± 0.79	8.18 ± 0.74	0.827	0.410
Mothers				
WBC count (× 10^3/mm^3)	15.64 ± 5.55	9.81 ± 3.79	6.696	< 0.001
Platelet count (× 10^3/mm^3)	221.38 ± 77.70	213.17 ± 56.95	0.658	0.512
MPV (fL)	8.79 ± 1.26	9.19 ± 1.03	1.946	0.054

Data are presented as mean ± SD.
CA: chorioamnionitis; WBC: white blood cells; ANC: absolute neutrophil count; MPV: mean platelet volume; SD: standard deviation.
$p < 0.05$: significant; $p < 0.01$: highly significant.
[a] Student's t-test.



AUC

Area	Std. error	Asymptotic significance	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.557	0.053	0.277	0.454	0.661

Figure 1. Receiver operating characteristic (ROC) curve for prediction of neonatal sepsis using mean platelet volume (MPV).
ROC: receiver operating characteristic; AUC: area under the curve.

in 2 cases while the third one developed poor feeding and hypoglycemia. A lumbar puncture was performed on these 3 infants, and no pathogen was isolated. All study group infants had negative blood cultures, including those who became symptomatic after admission. Forty-two (72%) patients in the CA group showed a significantly high CRP on day 1, with a notable decrease on day 3 ($p < 0.001$). Leukopenia was observed in only 4 infants (6%) of the CA group on day 1 and was associated with neutropenia in 2 cases. Laboratory data comparison of the CA-exposed infants on day 1 and day 3 is shown in **Tab. 3**. The antibiotic duration in CA-exposed infants ranged from 2-10 days, with a mean value of 5.69 ± 1.89, and no mortality was recorded until discharge time. Out of the 58 patients with CA, 32 (55%) mothers had PROM, and 47 (81%) received IAP. Maternal fever of 38.0°C or higher was documented in 32 (55%) patients on admission, the remaining 26 patients developed intrapartum fever afterward, while high vaginal swab (HVS) was positive in 18 (31%) mothers. The most commonly isolated organisms in HVS were GBS in 14 (24%) patients, *E. faecalis* in 2 patients, *E. coli* and *C. koseri* in one patient each. In addition to fever, maternal tachycardia was noted in 18 (31%) patients, fetal tachycardia was noted in 29 (50%) patients, and foul-smelling liquor was noted in 8 (14%) patients. In the CA group, maternal CRP was positive in 43 (74%) patients with a mean value of 64.3 ± 78.3. Maternal leukocytosis was a statistically significant finding in women with CA, compared to the control group (15.64 ± 5.55 vs. 9.81 ± 3.79; $p < 0.001$). Thrombocytopenia was noted in 10 (17%) women with CA, compared to 7 (11%) cases in the control group; however, this was statistically insignificant ($p > 0.05$). Placental histopathology specimens were reported in 12 (20%) patients and were positive for CA and/or funisitis in 8 (14%) patients, while the diagnosis was only clinically suspected in 46 (79%) women. Placental histopathology was performed in only one of the 3 symptomatic cases and was positive for funisitis.

Discussion

Although the incidence of neonatal EOS has dramatically decreased in the new era of IAP for all pregnant women at risk, infants exposed to maternal CA remain at potential risk of mortality and long-term morbidities. A recent practice adopted by some NICUs includes close monitoring with serial physical assessments of healthy term or near-term CA-exposed infants in maternity wards, without admission to the NICU, or administration of antibiotics. However, some initially healthy-appearing infants may be infected, and delayed commencement of antibiotic therapy is deleterious and may be fatal. Blood cultures and inflammatory markers, such as CRP, remain the cornerstone of neonatal EOS diagnosis. There is no single inflammatory marker capable of confirming or refuting neonatal sepsis. As suggested by some investigators, the combination of different markers like CRP, procalcitonin, and interleukin-6, may enhance the neonatal EOS laboratory diagnosis [17, 18]. The present study aimed to evaluate the role of MPV as an early adjuvant clinical marker of neonatal sepsis amongst asymptomatic CA-exposed infants. We found no evidence of significant MPV change in asymptomatic CA-exposed infants, compared to the healthy control group. The MPV in the study group was 8.29 ± 0.79 fL, compared to the control group (8.18 ± 0.74 fL), which are values comparable to normal reference ranges of 8.21 ± 0.65 fL reported in healthy infants [19]. High MPV, described in several previous studies related to EOS, was not observed in this study [20-22]. The MPV cut-off values in these studies ranged from 10.2 to 10.75 fL and were significantly correlated with neonatal sepsis. Nevertheless, our results were in agreement with those of the studies conducted

Table 3. Comparison between day 1 and day 3 investigations in the chorioamnionitis (CA)-exposed infants' group.

	WBC count		ANC		Platelet count		MPV		CRP	
	D1	D3	D1	D3	D1	D3	D1	D3	D1	D3
Mean	13.52	11.41	8.30	5.89	238.38	300.48	8.23	8.33	67.06	9.61
SD	6.10	5.28	5.21	4.15	67.65	118.60	0.85	0.82	52.15	4.69
t	1.277		1.695		2.760		0.599		4.423	
p-value	0.215		0.106		0.012		0.556		0.001	

WBC: white blood cells; ANC: absolute neutrophil count; MPV: mean platelet volume; CRP: C-reactive protein; D1: day 1; D3: day 3; SD: standard deviation.

by Aksoy et al. and Karne et al., who found no statistically significant MPV differences between healthy neonates and neonates with sepsis [23, 24]. Similarly, no statistical differences were found in platelet count, WBC count, or ANC between the two study groups. In the study group, 81% of the women received IAP based on suspected CA, and this explains the very low incidence of clinical EOS and negligible occurrence of proven sepsis in CA-exposed infants. In developed countries, the current incidence of culture-positive EOS ranges from 0.4-0.8 cases per 1,000 live-born term infants and is much lower in healthy asymptomatic infants [25]. Furthermore, the overall prevalence of CA affecting term infants during the study period is approximately 4.5 per 1,000 live births, which is quite lower than the reported data by other investigators, with a prevalence of 9.7-60 per 1,000 live births [8, 26]. In this study, CRP was significantly high in 72% of CA-exposed infants, and in 74% of the affected mothers. However, different studies acknowledge that, in fetal inflammatory response syndrome, secondary to CA, CRP and WBC count modestly increase in maternal and fetal blood, and have limited value for EOS diagnosis [27, 28]. The predictive value of CRP and WBC count indices is poor to diagnose early neonatal sepsis, and abnormal values are observed in uninfected infants [29]. Furthermore, histological CA was confirmed in 14% of women in the CA group and was associated with rising inflammatory markers and leukocytosis in the exposed infants, despite negative blood cultures, and this agrees with the results of previous investigations [30, 31]. Many clinicians still initiate and gauge antibiotics durations based solely on these numerical laboratory data regardless of the clinical well-being of infants and negative blood cultures [32]. Although the debatable guidelines of the AAP and the CDC for prevention of perinatal GBS are strictly followed in our unit and some other NICUs around the world, robust evidence is emerging to change them, with proven safety and efficacy. The newly reported data and quality improvement projects implementing the serial physical examination strategy for asymptomatic CA-exposed term or near-term infants, showed a substantial reduction of antibiotics exposure to less than 55%, without adverse outcomes [33, 34]. The use of neonatal sepsis calculator developed by Puopolo et al. to predict neonatal EOS utilizing the maternal risk factors has proven very effective in limiting the unnecessary use of antimicrobial agents in asymptomatic CA-exposed infants [35, 36]. Antibiotic administration, while protecting mothers and infants at risk, may lead to gut microbiome alteration, with long-term negative consequences, such as obesity, allergy, inflammatory bowel disease, and bronchial asthma [37, 38].

We acknowledge some limitations of our study, especially the small sample size and retrospective, single-center study design, which may have contributed to possible reporting bias. Maternal CA diagnosis was clinically assumed in most women, while histological CA was only reported in 14% of cases, with a possibility of inaccurate inclusion of some cases not fulfilling the Triple I diagnostic criteria.

Conclusion

This study showed that MPV is not a sensitive EOS marker in CA-exposed infants, despite its presumed reliability to predict neonatal invasive bacterial infection. Most of term and near-term CA-exposed infants are born to mothers receiving IAP and are unlikely to be infected or to have positive blood culture. Adequately powered multicenter studies are needed to evaluate MPV potential as a useful predictor of neonatal EOS.

Declaration of interest

The Authors have no potential conflicts of interest to disclose. The Authors have no financial relationships relevant to this article to disclose.

References

1. Hecht JL, Allred EN, Kliman HJ, Zambrano E, Doss BJ, Husain A, Pflueger SM, Chang CH, Livasy CA, Roberts D, Bhan I, Ross DW, Senagore PK, Leviton A. Histological characteristics of singleton placentas delivered before the 28th week of gestation. Pathology. 2008;40(4):372-6.
2. DiGiulio DB, Romero R, Kusanovic JP, Gómez R, Kim CJ, Seok KS, Gotsch F, Mazaki-Tovi S, Vaisbuch E, Sanders K, Bik EM, Chaiworapongsa T, Oyarzún E, Relman DA. Prevalence and diversity of microbes in the amniotic fluid, the fetal inflammatory response, and pregnancy outcome in women with preterm pre-labour rupture of membranes. Am J Reprod Immunol. 2010;64:38-57.
3. Pappas A, Kendrick DE, Shankaran S, Stoll BJ, Bell EF, Laptook AR, Walsh MC, Das A, Hale EC, Newman NS, Higgins RD; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research

Network. Chorioamnionitis and early childhood outcomes among extremely low-gestational-age neonates. JAMA Pediatr. 2014;168:137-47.
4. Polin RA; Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129(5):1006-15.
5. Committee on Infectious Diseases; Committee on Fetus and Newborn; Baker CJ, Byington CL, Polin RA. Policy statement-Recommendations for the prevention of perinatal group B streptococcal (GBS) disease. Pediatrics. 2011;128(3):611-6.
6. Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease – revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010;59(RR-10):1-36.
7. Carola D, Vasconcellos M, Sloane A, McElwee D, Edwards C, Greenspan J, Aghai ZH. Utility of early-onset sepsis risk calculator for neonates born to mothers with chorioamnionitis. J Pediatr. 2018;195:48-52.
8. Braun D, Bromberger P, Ho NJ, Getahun D. Low rate of perinatal sepsis in term infants of mothers with chorioamnionitis. Am J Perinatol. 2016;33(2):143-50.
9. Benitz WE, Wynn JL, Polin RA. Reappraisal of guidelines for management of neonates with suspected early-onset sepsis. J Pediatr. 2015;166(4):1070-4.
10. Higgins RD, Saade G, Polin RA, Grobman WA, Buhimschi IA, Watterberg K, Silver RM, Raju TN; Chorioamnionitis Workshop Participants. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis. Obstet Gynecol. 2016;127:426-36.
11. Hooven TA, Polin RA. Time to overhaul the "rule out sepsis" workup. Pediatrics. 2017;140(1):e20171155.
12. Oncel MY, Ozdemir R, Yurttutan S, Canpolat FE, Erdeve O, Oguz SS, Uras N, Dilmen U. Mean platelet volume in neonatal sepsis. J Clin Lab Anal. 2012;26(6):493-6.
13. Ramesh B Y. Platelet indices in neonatal sepsis: A review. World J Clin Infect Dis. 2017;7(1):6-10.
14. Prathyusha, Shreekrishna G. N, Sinchana B, Sahana B. Mean platelet volume (MPV) as a diagnostic marker in neonatal sepsis. Int J Contemp Pediatr. 2019;6(3):1036-40.
15. Shalaby M, Sobeih A, Abdulghany W, Behiry EG, Ismail YM, Abd-El-Aziz MA. Mean platelet volume and serum uric acid in neonatal sepsis: A case-control study. Ann Med Surg (Lond). 2017;(20):97-102.
16. Bhat R. Platelet indices in neonatal sepsis: A review. World J Clin Infect Dis. 2017;7(1):6-10.
17. Ozdemir AA, Elgormus Y. Diagnostic value of presepsin in detection of early-onset neonatal sepsis. Am J Perinatol. 2017;34(6):550-6.
18. Rashwan NI, Hassan MH, Mohey El-Deen ZM, Ahmed AE. Validity of biomarkers in screening for neonatal sepsis – A single centre – hospital based study. Pediatr Neonatol. 2019;60(2): 149-55.
19. Kim KY, Kim KE, Kim KH. Mean platelet volume in the normal state and in various clinical disorders. Yonsei Med J. 1986;27: 219-26.
20. Catal F, Tayman C, Tonbul A, Akça H, Kara S, Tatli MM, Oztekin O, Bilici M. Mean platelet volume (MPV) may simply predict the severity of sepsis in preterm infants. Clin Lab. 2014;60(7): 1193-200.
21. Kim CH, Kim SJ, Lee MJ, Kwon YE, Kim YL, Park KS, Ryu HJ, Park JT, Han SH, Yoo TH, Kang SW, Oh HJ. An increase in mean platelet volume from baseline is associated with mortality in patients with severe sepsis or septic shock. PLoS One. 2015;10(3):e0119437.
22. Tiwari R, Mahtabuddin AQR, Sharma RC. Study of mean platelet volume as predictive index of neonatal sepsis. Int J Biomed Res. 2017;8(04):220-3.
23. Aksoy H T, Eras Z, Guzoglu N, Canpolat FE, Dilmen U. Mean platelet volume is not associated with bacterial sepsis in newborns. Int J Infect Dis. 2013;17(12):e1263.
24. Karne TK, Joshi DD, Zile U, Patil S. Study of Platelet Count and Platelet Indices in Neonatal Sepsis in Tertiary Care Institute. MVP J Med Sci. 2017;4(1):55-60.
25. Fjalstad JW, Stensvold HJ, Bergseng H, Simonsen GS, Salvesen B, Rønnestad AE, Klingenberg C. Early-onset sepsis and antibiotic exposure in term infants: a nationwide population-based study in Norway. Pediatr Infect Dis J. 2016;35:1-6.
26. Malloy MH. Chorioamnionitis: epidemiology of newborn management and outcome United States 2008. J Perinatol. 2014;34(8):611-5.
27. Zanardo V, Peruzzetto C, Trevisanuto D, Cavallin F, Vedovato S, Straface G, Chiarelli S. Relationship between the neonatal white blood cell count and histologic chorioamnionitis in preterm newborns. J Matern Fetal Neonatal Med. 2012;25(12):2769-72.
28. Howman RA, Charles AK, Jacques A, Doherty DA, Simmer K, Strunk T, Richmond PC, Cole CH, Burgner DP. Inflammatory and haematological markers in the maternal, umbilical cord and infant circulation in histological chorioamnionitis. PloS One. 2012;7:e51836.
29. Hedegaard SS, Wisborg K, Hvas AM. Diagnostic utility of biomarkers for neonatal sepsis – a systematic review. Infect Dis (Lond). 2015;47(3):117-24.
30. Jackson GL, Engle WD, Sendelbach DM, Vedro DA, Josey S, Vinson J, Bryant C, Hahn G, Rosenfeld CR. Are complete blood cell counts useful in the evaluation of asymptomatic neonates exposed to suspected chorioamnionitis? Pediatrics. 2004;113(5):1173-80.
31. Wu HC, Shen CM, Wu YY, Yuh YS, Kua KE. Subclinical histologic chorioamnionitis and related clinical and laboratory parameters in preterm deliveries. Pediatr Neonatol. 2009;50(5):217-21
32. Kiser C, Nawab U, McKenna K, Aghai ZH. Role of guidelines on length of therapy in chorioamnionitis and neonatal sepsis. Pediatrics. 2014;133(6):992-8.
33. Joshi NS, Gupta A, Allan JM, Cohen RS, Aby JL, Kim JL, Benitz WE, Frymoyer A. Management of Chorioamnionitis-Exposed

Infants in the Newborn Nursery using a clinical examination-based approach. Hosp Pediatr. 2019;(9):4:227-33.

34. Jan AI, Ramanathan R, Cayabyab RG. Chorioamnionitis and Management of Asymptomatic Infants ≥35 Weeks Without Empiric Antibiotics. Pediatrics. 2017;140(1):e20162744.
35. Puopolo KM, Draper D, Wi S, Newman TB, Zupancic J, Lieberman E, Smith M, Escobar GJ. Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors. Pediatrics. 2011;128(5):e1155-63.
36. Dhudasia MB, Mukhopadhyay S, Puopolo KM. Implementation of the sepsis risk calculator at an academic birth hospital. Hosp Pediatr. 2018;8(5):243-50.
37. Saari A, Virta LJ, Sankilampi U, Dunkel L, Saxen H. Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. Pediatrics. 2015;135(4):617-26.
38. Ni J, Friedman H, Boyd BC, McGurn A, Babinski P, Markossian T, Dugas LR. Early antibiotic exposure and development of asthma and allergic rhinitis in childhood. BMC Pediatr. 2019;19:225.