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Fetal-Growth Phenotype and Early CRP Response During Evaluation for Early-Onset Neonatal Sepsis: A Retrospective Cohort Study

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Highlights

What are the main findings?

- Small-for-gestational-age (SGA) neonates undergoing evaluation for early-onset sepsis (EOS) had lower initial CRP concentrations than non-SGA neonates, despite similar maternal infectious risk and greater clinical instability.
- A significant SGA × EOS interaction was observed for both initial CRP and CRP dynamics, indicating that the fetal-growth phenotype modifies the early inflammatory response during EOS evaluation.

What are the implications of the main findings?

- The fetal-growth phenotype should be considered when interpreting CRP values during EOS evaluation, as CRP responses may not be comparable across growth categories.
- Prospective studies are needed to determine whether the fetal-growth phenotype influences the diagnostic performance and clinical utility of CRP-guided decision-making in neonatal sepsis.

Abstract

Background/Objectives: Early onset neonatal sepsis (EOS) is challenging because the clinical manifestations are not specific, and routinely used inflammatory biomarkers are influenced by non-infectious conditions especially during early neonatal transitioning time. Although the fetal-growth phenotype may alter immune system development, the effect on the acute phase response during suspected EOS remains poorly understood. The aim of this study was to determine whether fetal-growth phenotypes influence early CRP concentrations during EOS evaluation. Methods: We conducted a retrospective cohort study of newborns at ≥32 weeks of gestation who underwent on clinical and laboratory evaluation for EOS. Fetal-growth phenotypes were categorized as small-, appropriate-, or large- for gestational age (SGA, AGA, LGA). The EOS-positive group included neonates with either microbiologically confirmed EOS or clinically suspected EOS warranting antibiotic treatment. Serial C Reactive protein (CRP) values were used for a general linear model using

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gender, mode of delivery, and gestational age as covariates. Multivariable logistic regression was used to detect the effect of SGA on CRP-1 (value) and the antibiotic therapy relationship Results: Among 747 neonates, SGA infants had a lower initial CRP median (IQR) concentration compared to AGA and LGA [4.95(9.1), 7.03(9.7) and 6.2(14.4), $p < 0.05$]. Of 145 EOS-positive neonates, 7 had culture-confirmed infections, and 138 were classified as clinically suspected EOS based on clinical findings. The adjusted lnCRP-1 model was significant [F = 78.8, $p < 0.001$, ($R^2 = 0.38$)], and a significant interaction SGAxEOS was found. Among EOS-positive neonates, the estimated marginal mean lnCRP-1 was lower in SGA compared to non-SGA [1.51(95%CI: 1.19–1.82) versus 2.18 (95% CI: 2.04–2.32)]. **Conclusions**: SGA neonates display lower CRP concentrations during early EOS workout despite similar maternal risk factors and greater clinical instability. EOS-positive cases represented clinically suspected rather than culture-confirmed cases. These findings primarily reflect the early inflammatory response among newborns undergoing treatment for suspected EOS. The observed association between the fetal-growth phenotype and CRP concentrations warrants further investigation of CRP diagnostic performance across fetal-growth groups.

Keywords: fetal-growth phenotype; small for gestational age; immune system development; altered acute inflammatory response; C reactive protein; inflammatory biomarkers; early neonatal time; early onset sepsis

1. Introduction

Neonatal sepsis results in more than one half million deaths globally every year [1]. Sepsis is a life-threatening organ dysfunction due to abnormal host responses to infection [2]. Early-onset neonatal sepsis (EOS) is defined as suspected or confirmed systemic infection occurring within the first 72 h after birth. Culture-confirmed EOS requires the isolation of a pathogenic organism from blood or cerebrospinal fluid collected within 72 h after birth [3]. Clinical EOS was defined as compatible clinical signs and laboratory evidence of infection leading to antibiotic treatment, despite negative blood and cerebrospinal fluid cultures [4]. The strong predictive value of C-reactive protein (CRP) for mortality among newborns was revalidated lately in the context of poor performance of other markers such procalcitonin and Total Leucocyte count [5]. CRP remains one of the most widely used biomarkers in the neonatal population during EOS evaluation. However, CRP interpretation in clinical settings is complicated due to its physiological increase during the first hours after birth and well-established dependency on gestational age [6]. Furthermore, because CRP sensitivity increases over time, serial measurements are generally considered more specific than isolated determinants during sepsis evaluation among the neonatal population. On the other hand, CRP has important limitations including limited specificity in the absence of other clinical and laboratory abnormalities, and normal reference limits do not completely rule out underlying disease [7,8]. Clinical signs among neonates with EOS are often nonspecific and may overlap with non-infectious neonatal conditions especially in the early neonatal times. To mitigate the EOS diagnostic dilemma, several biomarkers including presepsin, interleukin-6, and endocan have been identified as promising better performance in the neonatal population. Nevertheless, their integration into routine clinical practice remains limited due to broad clinical validation [9–11]. Among these biomarkers, C-reactive protein has been widely adopted in clinical practice, although its interpretation is also influenced by noninfectious perinatal factors [12,13]. In the activated innate immune system sepsis pro-inflammatory and anti-inflammatory mediators are released followed by a rise in the level of acute phase molecules proposed as sepsis biomarkers [14]. In a

previous published study among healthy newborns at 48–72 h after birth, the authors described the serum concentration of CRP to be higher in the male gender, vaginally delivered, and born at a higher gestational age [13]. The neonatal CRP concentration varies according to both gestational age and postnatal age, with higher values reported among term neonates and a physiologic increase during the first days after birth [6,15]. Other non-infectious determinants of CRP concentrations among newborns younger than 72 h of age were: perinatal stress, neonatal illness, hypothermia, and respiratory morbidity [16–18]. Therapeutic hypothermia delays the C-reactive protein response and suppresses white blood cell and platelet counts among newborns detected to have neonatal encephalopathy [17].

Small-for-gestational-age (SGA) status, conventionally defined by birth weight below the 10th percentile for gestational age, is an anthropometric classification that includes both constitutionally small neonates and newborns affected by pathological fetal growth restriction [19]. Because constitutionally small neonates and infants affected by pathological fetal growth restriction may differ in their exposure to placental insufficiency, chronic intrauterine stress, and inflammatory programming, associations observed with SGA status should be interpreted within the context of this biological heterogeneity. Nevertheless, studies reporting differences in cord-blood immune biomarkers and placental gene expression suggest that, in some SGA neonates, an adverse intrauterine environment may modify developing immune and inflammatory pathways [20–22]. In the new article published by Darmstadt and Feldman, the authors highlight the link between fetal-growth phenotypes within a new developmental-programming framework [23]. Pregnancies affected by placental insufficiency, chronic intrauterine stress, hypoxia, and nutrient restriction will predispose SGA fetuses to compensatory inflammatory and catecholaminergic responses [24]. The mechanistic link between fetal-growth phenotype and CRP response is biologically plausible because placental insufficiency and chronic intrauterine stress have been associated with altered inflammatory signaling and immune programming in growth-restricted fetuses. These studies evaluated baseline neonatal inflammatory markers, placental biomarkers, or immune signaling pathways among IUGR neonates and were not conducted in the context of suspected neonatal sepsis. Interleukin-6 (IL-6) is the principal inducer of the acute-phase hepatic response and stimulates hepatocyte production of acute-phase proteins including CRP [25]. The liver is the primary target organ of this response, where IL-6-mediated signaling regulates protein synthesis of the acute-phase inflammatory state [26]. Therefore, altered cytokine signaling associated with fetal growth restriction could theoretically influence postnatal CRP responses. Although fetal growth restriction has been associated with abnormalities in inflammatory signaling and immune development, it remains unclear whether the fetal-growth phenotype influences CRP response during EOS evaluation. However, cytokine profiles, hepatic acute-phase regulation, and underlying molecular mechanisms were not directly assessed in the present study, and our findings should be interpreted as observational associations rather than evidence of a causal biological pathway.

To our knowledge, few studies have examined inflammatory biomarker responses in SGA neonates undergoing assessment for suspected EOS, and the potential interaction between the fetal-growth phenotype and EOS status on CRP concentrations has not been well characterized. Consequently, it is uncertain whether CRP values obtained during EOS evaluation convey comparable information across fetal-growth groups.

Primary Objective

To evaluate whether the fetal-growth phenotype is associated with the early inflammatory response, assessed using initial and dynamic CRP concentrations over time, among neonates undergoing clinical and laboratory evaluation for EOS.

Secondary Objectives

(i) To determine whether the association between the fetal-growth phenotype and early CRP response differs according to EOS status; and to (ii) explore if fetal-growth phenotype modifies the association between the CRP concentration and antibiotic initiation.

We hypothesized that an early CRP response would be different across birth weight for gestational age categories. We also hypothesized that the fetal-growth phenotype would modify the association between CRP-1 and antibiotic initiation.

2. Materials and Methods

2.1. Study Setting and Design

We conducted a retrospective observational design using data from neonates hospitalized in the Neonatal Department of the Mures County Hospital, a public academic affiliated maternity hospital with a Level II Neonatal Intensive Care Unit (NICU). Their unit provides comprehensive neonatal care for infants born at ≥32 weeks' gestation and transfers infants requiring complex or prolonged intensive care to a regional tertiary NICU. Approximately 50% of annual neonatal admissions undergo evaluation for presumed neonatal sepsis. The hospital serves as a referral center for lower-level maternity units located in southern and central Transylvania.

2.2. Participants

From 1 January to 31 December 2023, 1448 neonates were admitted into the hospital following birth. The primary analytic cohort included all neonates who underwent an evaluation within the first 24 h of life based on maternal risk factors, nonspecific clinical signs for EOS, or both. Overall, 747 neonates met the eligibility criteria and underwent serial clinical assessment, laboratory investigation, and microbiological testing in accordance with local clinical protocols updated on NICE guidelines 2021 [27]. The secondary analytic cohort consisted of neonates who underwent a subsequent CRP measurement because of persistent clinical concern, abnormal laboratory findings, or an evolving clinical condition.

2.3. Inclusion Criteria

(i) Neonates admitted to the nursery between 1 January and 31 December 2023, with GA ≥ 32 weeks, BW ≥ 1500 g and a baseline C-reactive protein (CRP) measurement documented within the first 24 h of life as part of a partial sepsis work-up.

(ii) Subsequently, entry into the secondary analytic cohort required the additional criterion of undergoing a second CRP measurement prior to reaching 48 h of age, performed due to persistent clinical concern, abnormal laboratory findings, or an evolving clinical condition.

2.4. Exclusion Criteria

(i) Neonates with GA < 32 completed weeks of gestation, birth weight < 1500 g, perinatal asphyxia (cord blood pH ≤ 7.00), major congenital structural anomalies, genetic disorders.

(ii) Neonates discharged or transferred to another institution 72 h of age and were excluded because complete follow up data were unavailable.

(iii) Additional exclusion criteria consist of a lack of gestational age determination based on first-trimester dating and missing necessary data on clinical, laboratory, microbiological outcome.

2.5. Exposure and Group Classification

Neonates were categorized by the birth weight for gestational age phenotype as: small for gestational age (SGA; <10th percentile), appropriate for gestational age (AGA; 10th–90th

percentile), and large for gestational age (LGA; >90th percentile). Birth weight percentiles were calculated using Fenton growth standards [28]. This birth-weight category served as the primary exposure variable.

EOS classification:

Cultured-confirmed EOS was defined in isolation of a recognized pathogenic microorganism from BC during EOS evaluation

Clinical EOS was defined as culture-negative neonates with persistent suspicion of infection following comprehensive assessment of maternal risk factors, neonatal clinical instability, laboratory abnormalities (including CRP, white blood cells, and neutrophils count), and overall clinical evaluation. In these cases, the attending neonatologist judged the likelihood of infection to be sufficiently high to warrant initiation/continuation of antibiotic therapy despite negative microbiological cultures.

EOS-negative status was defined to neonates in whom infection was considered unlikely after clinical and laboratory reassessment, resulting in antibiotic therapy being withheld.

Given the limited sensitivity of neonatal blood cultures, culture-negative neonates with persistent clinical suspicion following assessment of maternal infectious risk factors, neonatal clinical instability, laboratory abnormalities, and overall clinical evolution were classified as clinical EOS and included in the EOS+ group, although microbiological confirmation was unavailable. Antibiotic treatment was not initiated solely by elevated CRP values, but in conjunction with concurrent clinical symptoms and supportive diagnostic findings in accordance with local protocols based on NICE recommendations. The maternal risk score was calculated based on the presence of obstetrical risk factors for EOS from updated NICE criteria [28].

The neonatal instability score was calculated based on physiologic parameters of respiratory distress, hemodynamic instability, metabolic instability, and neurological signs.

For the maternal score, each of the 6 constituent parameters was evaluated binarily and assigned a value of 1 if present or 0 if absent. Similarly, the neonatal instability score was constructed using 9 separate parameters, each scored binarily as 0 or 1. Every item across both scores was weighted equally to reflect equivalent clinical importance, and no single parameter could receive a score higher than 1. All parameters were documented from the maternal and neonatal medical records. If any specific scores parameter was missing/unrecorded, it was not assigned 0 or 1 and was treated as missing data. Maternal and neonatal composite scores were unweighted and calculated based on the available items. Missing scoring parameters did not serve as exclusion criteria. These newly constructed scores served strictly as study-specific descriptors and were not externally validated.

To minimize information bias, all laboratory measurement values were retrieved from the institutional electronic database using predefined extraction criteria. Blood analyses were performed according to our hospital's standard of care. CRP levels were measured using an ARCHITECT c4000 Analyzer (Abbott Laboratories, Abbott Park, Illinois, USA). CRP concentrations in human serum were determined using a quantitative immunoturbidimetric method. The limit of detection was 0.1 mg/L, with a measuring range of 0.5–320 mg/L. The cutoff value of CRP above 15 mg/L is highly suspicious of EOS. All CRP concentrations included in analytical analysis were above the limit of detection (>0.1 mg/L). The in-hospital Microbiology Laboratory incubates blood cultures for 3–7 days in accordance with established guidelines [29,30].

The inclusion process for our study participants is illustrated in Figure 1. A data abstraction tool was developed to retrieve information essential to the study. All data were anonymized and assigned unique study codes before analysis.

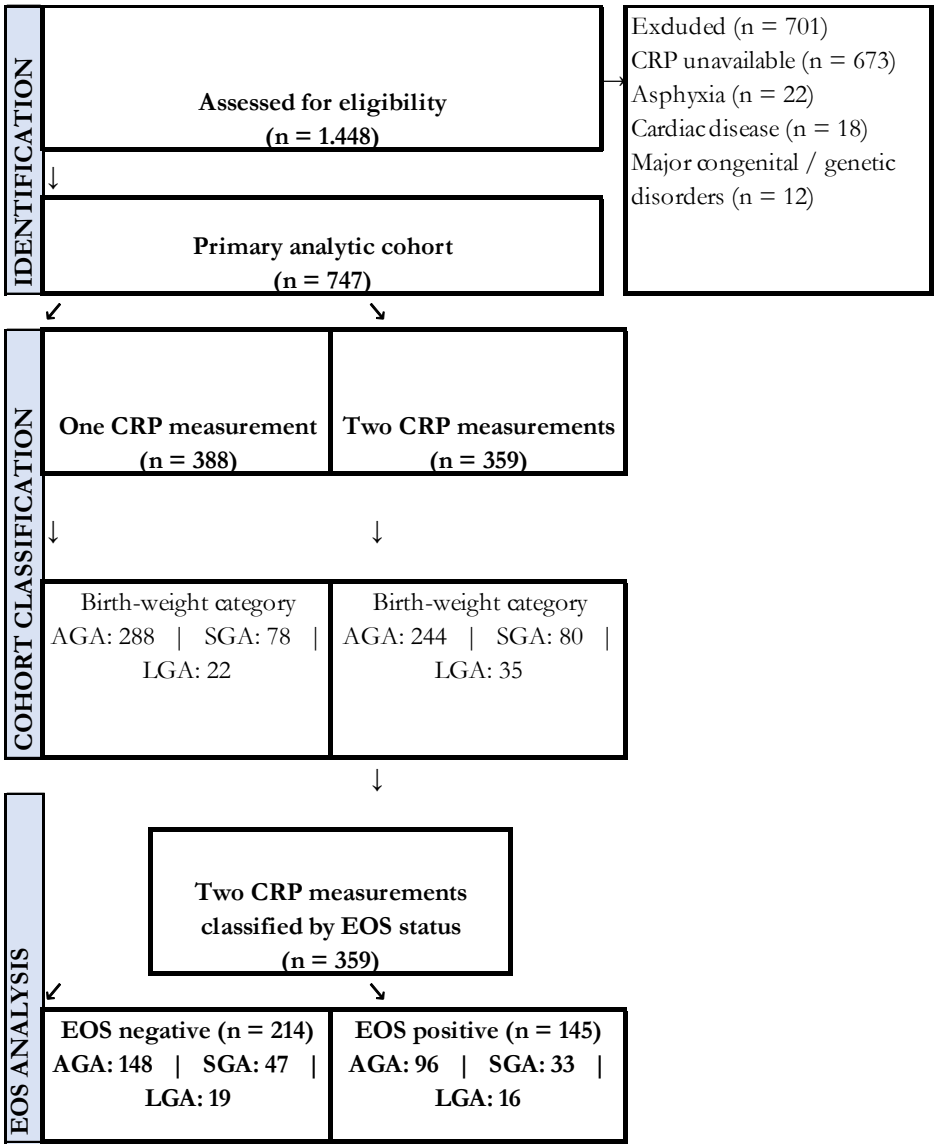


Figure 1. PRISMA-style participant flow. AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age; EOS, early-onset sepsis; CRP, C-reactive protein.

2.6. Variables Definition

Maternal risk factors for neonatal EOS:

i. Maternal fever during pregnancy: any documented maternal temperature (T ≥ 38.0 Celsius) during the third trimester.
ii. Intrapartum fever: maternal temperature ≥ 38.0 Celsius during labor.
iii. Maternal antibiotic exposure: receipt of systemic antibiotics during birth hospitalization.
iv. Prolonged rupture of membranes: interval from membrane rupture to delivery > 18 h in preterm births or >24 h in term births, in accordance with the institutional protocol [20].
v. Abnormal amniotic fluid: foul smelling, cloudy, and green-stained amniotic fluid.
vi. Maternal urinary tract infections: clinically diagnosed asymptomatic bacteriuria, acute cystitis, or pyelonephritis requiring antimicrobial treatment during pregnancy [24].

Neonatal instability score:

i. Thermal instability: temperature ≤ 36.5 °C or ≥38 °C unexplained by environmental conditions.
ii. Tachypnea or respiratory distress: respiratory rate > 80 breaths/min, grunting, and chest retractions.
iii. Apnea: documented cessation of breathing > 20 s.
iv. Abnormal heart rate: Heart rate ≤ 100 or ≥160 beats/min.
v. Poor feeding: feeding refusal, feeding intolerance, vomiting, excessive gastric residuals, or abdominal distension.
vi. Hypoglycemic: blood glucose < 35 mg/dL.
vii. Crying excessively: persistent inconsolable crying.
viii. Abnormal cry: weak or high-pitched cry.
ix. Lethargy: reduced activity, behavior, or responsiveness.

Laboratory

i. Culture-positive EOS: was defined as a positive blood culture for a recognized neonatal pathogen obtained during EOS evaluation.
ii. Abnormal leucocyte count was defined as <4000/mm^3, >20,000/mm^3
iii. Abnormal absolute neutrophils count was defined as <1750/or >14,500 cells/μL
iv. CRP-1 was the first CRP measurement obtained during the initial EOS evaluation within the first 24 h of life.
v. CRP-2 was the subsequent CRP measured within 48 h of age
vi. CRP change, ΔCRP was calculated as lnCRP-2 − lnCRP-1.

Antibiotic therapy was initiated by the attending neonatologist and was guided according to NICE recommendations [27]. Comprehensive assessment of maternal risk factors was performed by the attending obstetrician. Maternal and neonatal risk factors together with clinical signs suggestive of EOS served as primary rationale for antibiotic therapy initiation. Abnormal CRP, WBC, and TNC results were considered as adjunctive tools within the EOS workout to support the clinical assessment and were not employed as sole criteria for initiating antibiotic therapy.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania (approval No. 2476, 28 September 2023). The approval covered the retrospective review and analysis of medical records from neonates admitted between 1 January 2023 and 31 December 2023. Data extraction and analysis were performed retrospectively after completion of the study period.

Sample size and power

Because this retrospective study included all eligible neonates admitted during the predefined 12-month study period, no a priori sample-size calculation was performed. The investigation involved the use of all available data drawn from the medical records. Initially, a total of 1448 cases were identified. Among the initially screened neonates, 649 cases (44.8%) were excluded before eligibility assessment due to the absence of CRP measurements within the first 48 h of life classified as follows: 60 (9%) SGA, 532 (82%) AGA, and 57 (9%) LGA. After application of the eligibility criteria, a further 52 cases (3.6%) were excluded according to the predefined exclusion criteria, yielding the final study population. No cases were excluded due to missing data regarding specific parameters of the maternal and neonatal instability scoring system. Consequently, the primary cohort comprised 747 neonates, of whom 359 underwent a second CRP assessment. In the secondary cohort, 214 neonates were classified as EOS− and 145 cases as EOS+.

Statistical analysis

Descriptive analyses were first performed to characterize maternal demographics, obstetric risk factors, and neonatal clinical findings across fetal growth groups (SGA, AGA, and LGA). Continuous variables were summarized using means and standard deviations (SDs) and compared across groups using one way ANOVA. Categorical variables were summarized using counts and percentages and compared using chi square tests or Fisher's exact tests, as appropriate. All descriptive results were reported as absolute numbers, percentages, means, SD, medians, interquartile range, and corresponding p values. Because CRP values were markedly right skewed, all inferential analyses were conducted using logarithmic transformation to stabilize the variance of the residuals (lnCRP) rather than raw CRP values. Distributional properties were evaluated using histograms, skewness, kurtosis, and the Shapiro–Wilk test.

General Linear Models (GLMs). For multivariable analyses, the fetal-growth phenotype was coded as a binary variable (SGA versus non-SGA), with non-SGA neonates (AGA and LGA combined) serving as the reference category. This approach was chosen to specifically evaluate whether the SGA status was associated with differences in CRP response while preserving statistical power given the relatively small number of LGA neonates. To explore the relationship between CRP inflammatory responses amongst our population a general linear model (GLM) analyses were performed using ln CRP1, lnCRP2, and the change Δ CRP (lnCRP2-lnCRP1) as the dependent variable, whereas fetal growth, infectious status, and interaction were fixed effects. Three noninfectious factors (GA, male sex, mode of delivery) identified in the literature as important determinants of the outcome were included as covariates to adjust for potential confounders. Estimated marginal means and the corresponding 95% CI were calculated from the fitted model to compare adjusted outcome values across membership groups and infectious status, controlling for covariates. Pairwise comparisons were performed with Bonferroni adjustment for multiple testing. Model assumptions were assessed after inspection of residuals plots. As a sensitivity analysis, the GLM models were additionally adjusted for maternal age, maternal educational attainment, and maternal smoking status to evaluate the robustness of the observed associations among the fetal-growth phenotype, EOS status, and CRP concentrations. Logistic regression was used to explore the potential clinical implications of the observed CRP differences; a multivariable logistic regression model was constructed with antibiotic treatment for infection (yes/no) as the dependent variable. Independent variables included SGA, lnCRP-1, neonatal instability score, NICU admission, and the interaction term SGA × lnCRP-1. Adjusted odds ratio with the 95% CI were calculated. All tests were two-sided, and statistical significance was set at $p < 0.05$. Analyses were conducted using IBM SPSS Statistics for Windows, Version 29.0.2.0 (IBM Corp., Armonk, New York, NY, USA)

3. Results

The primary cohort comprised 532 AGA neonates (71.2%), 158 SGA neonates (21.2%), and 57 LGA neonates (7.6%). A comparison between included and excluded neonates according to the availability of at least one CRP measurement is presented in Supplementary Table S1. The secondary cohort comprised 244 AGA neonates (68.0%), 80 SGA neonates (22.3%), and 35 LGA neonates (9.7%). Characteristics of neonates undergoing one versus two CRP measurements are summarized in Supplementary Table S2. Among the 145 EOS+ neonates, 96 were AGA (66.2%), 33 were SGA (22.8%), and 16 were LGA (11.0%). Detailed clinical characteristics of EOS− and EOS+ neonates in the serial CRP cohort (N = 359) are provided in Supplementary Table S3.

Among EOS+ neonates, we had 7 cases overall with positive blood cultures: 4 cases *Escherichia coli*, 2 cases *Klebsiella pneumonia,* and 1 case *Acinetobacter baumannii*. No deaths or meningitis were recorded among included cases. Nonparametric comparisons of continuous

clinical and laboratory variables between EOS− and EOS+ neonates undergoing serial CRP assessment are shown in Supplementary Table S4.

3.1. Univariate Descriptive Analysis

Maternal and neonatal characteristics differ across fetal-growth groups (Table 1). SGA-mothers were younger, more frequent smokers, and had lower educational attainment, whereas the maternal EOS risk score did not differ significantly between fetal-growth groups. SGA neonates exhibited greater clinical instability, lethargy, hypoglycemia, thermal abnormalities, abnormal heart rate, and NICU admissions. Despite these differences in clinical presentation and positive blood cultures, antibiotic treatment and abnormal WBC were not significantly different across fetal-growth categories. CRP-1 was lower among SGA neonates compared with AGA and LGA neonates, whereas CRP-2 was not significantly different among fetal-growth groups.

Table 1. Maternal, neonatal, and CRP characteristics according to the fetal-growth phenotype among neonates evaluated for early-onset sepsis.

	SGA ***n* = 158**	**AGA** ***n* = 532**	**LGA** ***n* = 57**	***p*** **Value**
Maternal characteristics				
Maternal age, Median (IQR), Min-Max	23 (14) 14–41	27 (11) 13–45	31 (9) 19–41	0.001
Rural residence	95 (60.1)	341 (64.1)	31 (54.4)	0.2
Maternal education, years	8.6 (5.6)	10.5 (5.2)	12.1 (4.8)	0.001
Married/cohabiting	59 (37.3)	287 (53.9)	39 (68.4)	0.001
Smoking	68 (43.1)	132 (24.8)	10 (17.5)	0.001
Gravidity	2.4 (1.9)	2.6 (1.8)	2.7 (1.6)	0.4
Parity	1.9 (1.2)	1.9 (1.1)	2.01 (1.2)	0.5
Gestational diabetes	3 (1.9)	13 (2.5)	8 (14)	0.03
Gestational anemia	39 (24.5)	120 (22.5)	14 (24.5)	0.8
Gestational hypertension	13 (8.2)	23 (4.3)	7 (12.3)	0.04
Gestational age (weeks)	38.2 (1.7)	38.4 (1.6)	38.1 (1.6)	0.4
Latency interval, hours (SD)	8.3 (8.1)	7.6 (10.9)	6.3 (7.6)	0.6
Latency interval > 18 h	8 (5)	20 (3.7)	0	0.2
Maternal UTI	13 (8.2)	104 (19.5)	10 (17.5)	0.004
Intrapartum fever ≥ 38 °C	3 (1.9)	4 (0.75)	1 (1.7)	0.8
Maternal antibiotic therapy	13 (8.2)	43 (8.1)	2 (3.6)	0.4
Abnormal amniotic fluid	24 (15.2)	72 (13.5)	10 (17.5)	0.6
Cesarean delivery	65 (41.1)	209 (39.3)	31 (54.4)	0.08
Maternal risk score Median (IQR)	0 (1)	1 (1)	1 (1)	0.13

Table 1. *Cont.*

Vertex presentation	145 (91.8)	511 (96.1)	53 (93)	0.2
Apgar 1 min	8.9 (1.1)	9.1 (1.01)	8.9 (0.9)	0.19
Apgar 5 min	9.5 (0.9)	9.7 (0.6)	9.6 (0.7)	0.01
Birth weight, grams	2440 (317)	3217 (408)	3961 (538)	0.001
Length, cm	49.3 (2.5)	52.7 (2.2)	55.1 (2.3)	0.001
Head circumference, cm	31.6 (1.4)	33.5 (1.5)	35.1 (1.6)	0.001
Neonatal characteristics and outcomes				
Sex (male)	71 (44.9)	297 (55.8)	41 (71.9)	0.001
Thermal instability	45 (28.5)	90 (16.9)	14 (24.6)	0.004
Tachypnea	10 (6.3)	32 (6)	5 (8.8)	0.7
Poor feeding	6 (3.8)	20 (3.8)	2 (3.5)	0.9
Crying excessively	11 (7)	21 (4)	6 (10.5)	0.04
Weak cry	3 (1.9)	3 (0.6)	0	0.2
Lethargy	28 (17.7)	22 (4.1)	2 (3.5)	0.001
Hypoglycemia, *n* (%)	14 (8.9)	10 (1.9)	3 (5.3)	0.001
Abnormal heart rate	57 (36.1)	23 (4.3)	3 (5.3)	0.001
Neonatal instability score Median (IQR) (Min-Max)	1 (1) (0–8)	1 (1) (0–7)	1 (2) (0–5)	0.01
Antimicrobial therapy, *n* (%) No antimicrobial therapy Empiric therapy for <120 h Prolonged therapy ≥ 120 h	 125 (79.1) 24 (15.2) 9 (5.7)	 436 (81.9) 83 (15.6) 13 (2.4)	 41 (71.9) 14 (24.6) 2 (3.5)	 0.17
Blood culture positive	4 (2.53)	3 (0.56)	0	0.048
Abnormal WBC	17 (10.8)	62 (11.6)	6 (10.5)	0.6
Abnormal TNC	11 (7.0)	43 (8.1)	9 (15.7)	0.1
NICU admission, *n* (%)	55 (34.8)	82 (15.4)	10 (17.5)	0.001
Laboratory tests				
CRP-1 (mg/L), Median (IQR)	4.95 (9.16)	7.03 (9.78)	6.2 (14.49)	0.02
lnCRP-1, Median (IQR)	1.61 (2.2)	1.96 (1.56)	1.84 (1.69)	0.05
Neonatal age (hours) at CRP-1 measurement, Median (Q1-Q3)	18.2 (6–24)	16.5 (8–24)	16.6 (8–24)	0.5
Secondary analytic cohort				
	SGA *n*= 80	**AGA *n*= 244**	**LGA *n*= 35**	*p* value
CRP-2 (mg/L), Median (IQR)	3.19 (8.36)	4.24 (5.48)	4.50 (4.02)	0.61

Table 1. *Cont.*

lnCRP-2, Median (IQR)	1.19 (2.39)	1.46 (1.33)	1.52 (0.89)	0.1
ΔCRP, Median, (IQR)	0.35 (1.1)	0.44 (1.1)	0.41 (1.2)	0.34
Neonatal age (hours) at CRP-2 measurement, Median (Q1-Q3)	42 (38–42)	40.5 (36–42)	43.5 (40–46)	0.3
Time between the measurements (hours), Median (Q1-Q3)	22.8 (20–24)	23.5 (19–24)	26.9 (22–28)	0.5

Data are presented as *n* (%), mean (SD), or median (IQR); (Q1-Q3) as indicated. lnCRP-1 = natural logarithm of CRP-1; lnCRP-2 = natural logarithm of CRP-2; ΔCRP = lnCRP-2 − lnCRP-1; SGA = small for gestational age; AGA = appropriate for gestational age; LGA = large for gestational age; IQR = interquartile range; WBC = white blood cell count; TNC = total neutrophil count; UTI = urinary tract infection; SD = standard deviation, NICU = Neonatal Intensive Care Unit, CRP= C-reactive protein.

3.2. General Linear Model of Inflammatory Response

GLM models were fitted to examine the predictors of the outcome (lnCRP-1, lnCRP-2, and the change ΔCRP) after adjustment for GA, gender, and mode of delivery. For lnCRP1, the overall model was significant [$F = 78.8$, $p < 0.001$, (adjusted $R^2 = 0.38$)]. In the adjusted models, the fetal-growth phenotype was entered as a binary variable (SGA versus non-SGA), with non-SGA infants serving as the reference group. A significant SGA × EOS interaction indicated that the association between EOS status and lnCRP-1 differed according to the SGA status. The GA, sex, and mode of delivery were also independently associated with lnCRP-1. A sensitivity analysis additionally adjusting for maternal age, maternal educational attainment, and maternal smoking status yielded materially unchanged results. In the fully adjusted model, the SGA status ($F = 7.75$, $p = 0.006$), EOS status ($F = 98.04$, $p < 0.001$), and SGA × EOS interaction ($F = 9.40$, $p = 0.002$) remained independently associated with lnCRP-1. Maternal age, educational attainment, and smoking status were not independently associated with lnCRP-1. For lnCRP-2, the overall model was significant [$F = 38.3$, $p < 0.001$, (adjusted $R^2 = 0.38$)]. EOS and GA remained significantly associated with lnCRP-2. The SGA status and SGA × EOS interaction were not significant. For lnCRP-2, additional adjustment for maternal age, maternal educational attainment, and maternal smoking status produced similar findings. The EOS status remained significantly associated with the outcome ($F = 13.91$, $p < 0.001$), whereas the SGA status ($F = 2.56$, $p = 0.110$) and SGA × EOS interaction ($F = 0.008$, $p = 0.929$) remained non-significant. Maternal age, educational attainment, and smoking status were not independently associated with lnCRP-2. The third model evaluating the dynamics of ΔCRP yielded an $F = 4.8$, $p < 0.001$, adjusted $R^2 = 0.06$. Although neither the SGA status nor EOS status alone was significantly associated with ΔCRP, the interaction of SGA × EOS remained significant. The gestational age, sex, and mode of delivery were not significantly associated with ΔCRP (Table 2). For ΔCRP, additional adjustment for maternal age, maternal educational attainment, and maternal smoking status confirmed the primary results. The SGA × EOS interaction remained significantly associated with ΔCRP after adjustment ($F = 4.17$, $p = 0.042$), whereas neither the SGA status ($F = 1.39$, $p = 0.240$) nor EOS status ($F = 1.89$, $p = 0.171$) were independently associated with the outcome. Maternal age, educational attainment, and smoking status were not independently associated with ΔCRP, supporting the robustness of the primary findings.

Table 2. General linear models for lnCRP-1, lnCRP-2, and ΔCRP.

Predictor	lnCRP-1 (n = 747)	p	lnCRP-2 (n = 359)	p	ΔCRP (n = 359)	p
SGA	11.797	0.001	2.25	0.13	3.24	0.07
EOS	104	0.001	15.4	0.001	1.51	0.22
SGA × EOS	12.8	0.001	0.16	0.7	7.06	0.008
Gestational age	175	0.001	169	0.001	2.82	0.09
Male sex	9.4	0.002	0.139	0.7	0.31	0.57
Mode of delivery	8.9	0.003	0.51	0.4	2.08	0.15
Overall model F	78.8	0.001	38.3	0.001	4.8	0.001
Model R^2	0.39		0.39		0.07	
Adjusted R^2	0.38		0.38		0.06	

Values shown for each predictor are F statistics with corresponding p values. lnCRP-1 = natural logarithm of CRP-1; lnCRP-2 = natural logarithm of CRP-2; ΔCRP = lnCRP-2 − lnCRP-1; SGA = small for gestational age; EOS = early-onset sepsis, CRP = C-reactive protein.

Among EOS- neonates, adjusted lnCRP-1 was similar across fetal-growth categories. In contrast, among EOS+ neonates, SGA cases displayed substantially lower ln-CRP1 compared to non-SGA counterparts; differences in ln-CRP2 were attenuated. Among EOS+ neonates, SGA infants also exhibited a smaller log-scale CRP increase than EOS + non-SGA infants. Estimated marginal means are presented in Table 3.

Table 3. Estimated marginal means (95% CI) for lnCRP-1 in the primary cohort and for lnCRP-2 and ΔCRP in the restricted cohort, according to SGA and EOS status.

	SGA Mean (95% CI)	Non-SGA Mean (95% CI)
lnCRP-1		
EOS-	0.81 [0.73, 0.89]	0.82 [0.76, 0.88]
EOS +	1.51 [1.19, 1.82]	2.18 [2.04, 2.32]
lnCRP-2		
EOS-	0.86 [0.61, 1.19]	1.04 [0.95, 1.13]
EOS +	1.37 [1.01, 1.68]	1.38 [1.12, 1.64]
ΔCRP		
EOS-	0.35 [0.08, 0.61]	0.25 [0.13, 0.37]
EOS+	0.17 [−0.15, 0.51]	0.75 [0.58, 0.92]

EOS = early-onset sepsis; SGA = small for gestational age; CRP = C-reactive protein, lnCRP-1 = natural logarithm of CRP-1; lnCRP-2 = natural logarithm of CRP-2; ΔCRP = lnCRP-2 − lnCRP-1; CI = confidence interval.

3.3. Logistic Regression- Exploratory Analysis of Antibiotic Initiation

A multivariable logistic regression model was used to test the predictors of the antibiotic treatment. lnCRP-1, neonatal instability score, and NICU admission were independently associated with the outcome. The SGA status was associated with lower odds (aOR 0.04, 95% CI 0.01–0.22). The interaction of SGA × ln-CRP1 was significant [aOR 0.27, 95% CI (0.13–0.56)], Omnibus χ^2 (5) = 291.5, $p < 0.001$ Nagelkerke R^2 = 0.515. Specifically, the effect of increasing CRP-1 on the probability of treatment initiation was attenuated among SGA neonates compared to non-SGA counterparts (Table 4 and Figure 2).

Table 4. Predictors of initiating antimicrobial therapy.

	Antimicrobial Therapy
Predictor	**AOR [95% CI]**
NICU admission	7.71 [3.54, 16.87]
lnCRP-1	7.12 [5.04, 10.07]
Neonatal instability score	2.49 [2.08, 3.00]
SGA	0.04 [0.01, 0.22]
SGA × lnCRP-1	0.27 [0.13, 0.56]

AOR= adjusted odds ratio, lnCRP-1= natural logarithm of CRP-1, CI = confidence interval, SGA= small for gestational age, NICU = neonatal intensive care unit, CRP = C-reactive protein.

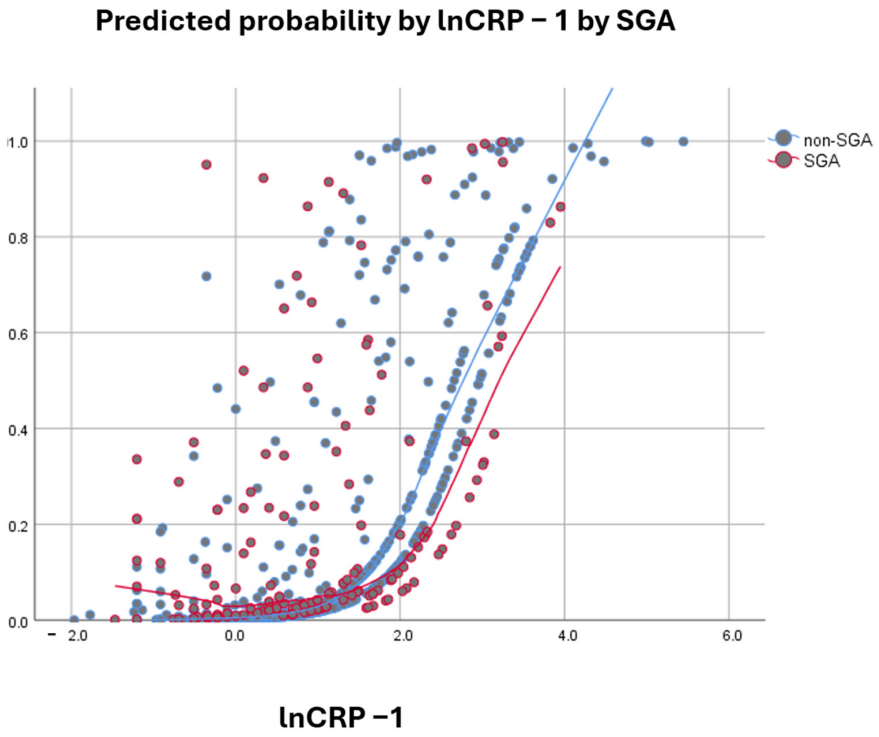


Figure 2. Probability of initiating antimicrobial therapy according to CRP-1 and SGA status.

4. Discussion

The principal finding of this study was that the SGA phenotype was associated with differences in the early CRP response during EOS evaluation. SGA neonates demonstrated lower CRP-1 and altered CRP trajectories despite comparable maternal EOS risk scores and greater clinical instability. These differences were most apparent among EOS+ neonates and were reflected by significant interaction of SGA × EOS on both CRP-1 and ΔCRP. Collectively, these findings suggest an association between the fetal-growth phenotype and the early CRP response during EOS evaluation.

The observed CRP pattern is biologically plausible. Experimental and clinical studies suggest that chronic intrauterine stress and placental insufficiency may alter immune development and inflammatory signaling [31]. Abnormal postnatal immune responsiveness after IUGR has been described in one experimental model directly tested immune cell responses after ex vivo stimulation; [32] the authors interpreted the overall phenotype as moderate suppression of postnatal immune response in IUGR piglets. This result is

consistent with our finding that SGA modulates CRP dynamics among neonates evaluated for EOS, even though it does not support the effect of the interaction of SGA × EOS. Another study using a murine model, IUGRF cases exhibited altered pro-inflammatory response following lipopolysaccharide-induced endotoxemia, suggesting blunt innate immune response to a sepsis-like challenge [33]. Although our study was not designed to investigate underlying mechanisms, these experimental findings provide biological plausibility for an altered acute-phase response among SGA neonates. However, they do not directly establish the mechanism or direction of the CRP response observed in our cohort.

Several observations suggest that the lower CRP concentrations observed among SGA infants were unlikely to be solely explained by lower illness severity. Maternal EOS risk scores did not differ across fetal-growth groups, whereas SGA infants exhibited greater clinical instability and more frequent NICU admission. Furthermore, differences in the CRP response were predominantly observed among infants managed as EOS+, whereas baseline CRP values among EOS- infants were largely similar across fetal-growth groups. These findings are consistent with differences in the inflammatory response rather than differences in risk exposure alone. Nevertheless, because microbiologically confirmed EOS was uncommon, residual differences in disease severity cannot be completely excluded.

Our exploration analysis examined whether the observed CRP differences had potential clinical implications. The initial CRP concentration was strongly associated with antibiotic initiation, but the relationship differed according to the fetal-growth phenotype. Specifically, the association between CRP-1 and antibiotic treatment was significantly weaker among SGA infants. Although this finding cannot establish differences in physician decision-making or treatment bias, it suggests that CRP values may not convey equivalent clinical information across fetal-growth groups. Because antibiotic initiation was determined by clinicians using a combination of maternal risk factors, neonatal clinical findings, laboratory results, and overall clinical assessment, the observed interaction should be interpreted as reflecting patterns of treatment allocation within our cohort rather than direct evidence of differential CRP diagnostic performance across fetal-growth groups.

Importantly, our findings do not establish that incorporation of the fetal-growth phenotype improves the diagnostic performance or clinical utility of CRP during EOS evaluation. Future prospective studies should evaluate CRP diagnostic accuracy across fetal-growth groups, including sensitivity, specificity, and predictive performance, before modifications to clinical interpretation or decision-making can be recommended. The robustness of these findings was further supported by sensitivity analyses incorporating maternal age, maternal educational attainment, and maternal smoking status, which yielded materially unchanged results across all GLM models.

In addition to the fetal-growth phenotype and EOS status, gestational age emerged as the strongest independent determinant of both CRP-1 and CRP-2. Gender, GA, and mode of delivery were independently associated with CRP-1 but not with CRP-2. These findings are consistent with previous studies [5,14] demonstrating that non-infectious perinatal factors influence neonatal CRP concentrations during the first days of life and should be considered when interpreting inflammatory biomarkers during EOS evaluation [34,35].

Inconsistent with our findings, in a small cohort term and near-term SGA neonates had higher CRP values measured from the cord blood compared to AGA neonates, suggesting an altered inflammatory state at birth before the postnatal CRP response; however, that study did not evaluate postnatal CRP trajectories or responses to EOS [36]. Consistent with our results, a study examining the broader immune biomarkers among healthy SGA neonates identified relationships between the SGA status and lower IL-1beta, brain-derived neurotrophic factor, and neurotrophin-3. However, this study supports an altered im-

mune response among SGA neonates, not a direct CRP difference between fetal-growth phenotypes [22].

Several limitations should be acknowledged. First, because CRP measurements were obtained according to clinical practice rather than a predefined study protocol, a substantial number of neonates were excluded before eligibility assessment. The distribution of fetal-growth phenotypes among included neonates differed from that of the source population, with SGA infants being overrepresented in the analytical cohort. This may have introduced selection bias and could limit the generalizability of the findings. Furthermore, repeat CRP measurements were obtained according to clinical indications rather than according to a standardized study protocol. Consequently, analyses involving CRP-2 and ΔCRP may be subject to indication bias, as neonates undergoing repeat testing likely represented a subgroup with greater clinical concern, abnormal laboratory findings, or evolving clinical conditions. In addition, the single-center design and the exclusion of very preterm infants (<32 weeks' gestation), neonates with birth weight < 1500 g, and critically ill newborns may limit the applicability of these findings to higher-risk neonatal populations. The exact time of CRP measurement relative to symptom onset, BC sampling, and antibiotic initiation was not documented consistently in medical records and therefore could not be evaluated. However, BC samplings were obtained before the initiation of antibiotic therapy in all cases according to institutional practices. A potential source of incorporation bias should be acknowledged since CRP was part of the clinical evaluation used to identify infants with suspected EOS. However, empirical therapy was initiated primarily based on maternal, neonatal risk factors, and neonatal clinical instability; therefore, the potential impact of the incorporation bias related to CRP is likely to be limited. Finally, EOS+ misclassification bias is another potential limitation of this study. In the absence of a positive BC, some cases may have been incorrectly classified with respect to true EOS. Only seven EOS-positive neonates had a culture-confirmed infection, limiting our ability to evaluate associations specifically within microbiologically confirmed EOS. Although BC is considered as the reference standard for EOS, it has limited sensitivity in the neonatal population [37]; in clinical practice, EOS+ relies on a combination of clinical findings, perinatal risk factors, and inflammatory markers, while microbiological confirmation is unavailable [38]. Finally, the SGA status is widely used in neonatal research even if did not distinguish constitutionally small neonates from those affected by fetal growth restriction. Doppler parameters and antenatal dimensional ultrasound were not consistently available for this retrospective study; therefore, fetal growth-restricted criteria could not be applied. It is possible that biological heterogeneity within our SGA sample may have obscured the association between the fetal-growth phenotype and CRP response.

This single-center study had an important sampling volume, and CRP measurements were serial. The recruitment period was relatively short, and the academic affiliation warrants adherence to standardized EOS management protocols among a vulnerable homogenous population. Although the timing of CRP measurements was similar across fetal -growth phenotype groups, residual variance in the sampling time and CRP kinetics may have influenced the observed association. This study addresses the relationship between fetal-growth phenotypes and the early CRP response during EOS evaluation for which the available evidence is limited. The fetal-growth phenotype was associated with early CRP concentrations during EOS evaluation. Further multicenter setting design studies incorporating IUGR ultrasound criteria are needed to determine whether these differences have implications for CRP diagnostic performance and clinical decision-making across fetal-growth groups.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/children13121642/s1, Table S1-title: Comparison of neonates

included and excluded according to availability of at least one CRP measurement, Table S2-title: Characteristics of neonates with one versus two CRP measurements, Table S3- title: Characteristics of EOS- and EOS+ neonates with serial CRP cohort (N=359), Table S4-title: Comparison of continuous variables between EOS + and EOS- neonates undergoing serial CRP assessment.

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Informed Consent Statement: Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

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Abbreviations

The following abbreviations are used in this manuscript:

AGA	Appropriate for gestational age
AOR	Adjusted odds ratio
CI	Confidence interval
CRP	C Reactive Protein
EOS	Early onset sepsis
GA	Gestational age
IQR	Interquartile range
IUGRF	Intrauterine growth-restricted fetuses
LGA	Large for gestational age
ln	Natural logarithm
Max	Maximum
Min	Minimum
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
OR	Odds ratio
SD	Standard deviation
SGA	Small for gestational age
TNC	Total neutrophils count
UTI	Urinary tract infection
WBC	White blood cells

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