ГЕСТАЦИОННЫЙ ВОЗРАСТ КАК ДЕТЕРМИНАНТА СОЗРЕВАНИЯ КИШЕЧНОЙ МИКРОБИОТЫ И УРОВНЯ МАГНИЯ В СЫВОРОТКЕ КРОВИ У НОВОРОЖДЁННЫХ

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АННОТАЦИЯ

Гестационный возраст является ключевым показателем биологической зрелости новорождённого и связан с формированием кишечного микробиоценоза, иммунной регуляции и нутритивно-метаболического статуса. Проведен вторичный анализ данных 125 новорождённых, распределённых на группы 26–31 нед (n=56), 32–36 нед (n=25) и ≥37 нед (n=44). Оценены показатели микробиоты (E. coli norm, UPE, Staph. epid./sap., Lactobacillus, Bifidobacterium; log) и маркёры IL-1β, IgA, витамина D и магния. С увеличением гестационного возраста отмечалось снижение IL-1β и условно-патогенной флоры и рост витамина D, магния, Lactobacillus и Bifidobacterium. Наиболее последовательные различия между всеми тремя группами выявлены для магния и Lactobacillus.

Ключевые слова: гестационный возраст; новорождённые; микробиота кишечника; IL-1β; IgA; витамин D; магний; Lactobacillus; Bifidobacterium; UPE.

GESTATIONAL AGE AS A DETERMINANT OF GUT MICROBIOTA MATURATION AND SERUM MAGNESIUM IN NEWBORNS

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ABSTRACT

Gestational age is an important indicator of biological maturity and is closely associated with the development of the intestinal barrier, immune regulation, and early formation of the gut microbiota. A secondary analysis of aggregated data from 125 newborns was performed, divided into the following groups: 26–31 weeks of gestation (n=56), 32–36 weeks (n=25), and ≥37 weeks (n=44). Indicators of the gut microbiota were evaluated (logarithmically transformed values of E. coli, opportunistic enterobacterial flora, Staphylococcus epidermidis/saprophyticus, Lactobacillus, Bifidobacterium), as well as immuno-metabolic markers (IL-1β, IgA, vitamin D, magnesium). As gestational age increased, a decrease in IL-1β levels and opportunistic enterobacterial flora was observed, whereas concentrations of vitamin D and magnesium, as well as the abundance of Lactobacillus and Bifidobacterium, increased. The results of the Kruskal–Wallis test with subsequent Dwass–Steel–Critchlow–Fligner post-hoc analysis and Spearman correlation analysis confirmed this maturation pattern. At the same time, magnesium and Lactobacillus demonstrated stepwise differences between all three gestational groups.

Keywords: gestational age; newborns; gut microbiota; IL-1β; IgA; vitamin D; magnesium; Lactobacillus; Bifidobacterium; opportunistic enterobacterial flora.

RELEVANCE:

Preterm birth remains one of the major causes of neonatal morbidity, since the biological systems that ensure postnatal adaptation—the intestinal

barrier, immune regulation, and metabolic homeostasis—do not have time to fully mature by the term gestational age. The neonatal period is characterized by rapid changes in nutrient intake, microbial exposure, and inflammatory reactivity, and these transitions are particularly difficult for infants born at lower gestational ages. Therefore, gestational age is an integral indicator of biological maturity and, in the clinical interpretation of early microbiological and laboratory phenotypes, is more informative than birth weight by itself [23].

Early intestinal colonization follows a certain developmental sequence that is shaped by the mode of delivery, type of feeding, environmental factors, and the degree of organismal maturity [22,24]. Studies of microbiome development in infants show that microbial communities change along a regular trajectory during the first weeks and months of life, and this trajectory is sensitive to both internal (host-related) and external factors [23,25]. In preterm infants, delayed establishment of obligate anaerobes and a higher relative abundance of opportunistic taxa, including enterobacteria and staphylococci, are frequently observed, which may contribute to the development of dysbiosis-associated inflammation and adverse outcomes [26,27]. Importantly, a number of studies indicate an association even of the earliest “primary” microbial signals (for example, meconium-associated patterns) with gestational age, supporting the concept of an influence of biological maturity on colonization already in the earliest postnatal window [28].

Since gestational age is closely linked to intestinal permeability, maturation of the immune system, and the intensity of exposures in neonatal intensive care settings, it should be considered a primary stratification factor in studies analyzing neonatal microbiota indices and associated immunological markers [21,26]. In parallel with microbiota maturation, the immunometabolic profile of newborns also undergoes significant changes along the gestational age gradient. Magnesium is a key intracellular cation involved in enzymatic

reactions, neuromuscular excitability, and metabolic regulation, and magnesium levels in newborns may reflect both physiological maturity and perinatal exposures [1,3]. Classical neonatal studies describe systematic fluctuations in serum magnesium concentrations in the early postnatal period and differences between preterm and term infants, underscoring the instability of mineral homeostasis immediately after birth [2,8].

From a clinical perspective, magnesium status is also relevant because magnesium sulfate is widely used in obstetric practice (for example, in severe preeclampsia/eclampsia and for fetal neuroprotection), and maternal treatment may influence neonatal magnesium levels and early adaptation [15–18]. Randomized trials and subsequent analyses have identified key perinatal situations in which magnesium sulfate is administered before preterm delivery, emphasizing the need to interpret neonatal magnesium indicators within a framework of gestational age stratification [16,17]. In addition, nutritional strategies in infants with very low birth weight (including the use of fortified human milk) may affect mineral balance, further supporting the inclusion of metabolic markers in phenotyping of neonatal maturity [6,7].

Despite growing interest in the neonatal microbiota and micronutrient status, many publications and local datasets still use heterogeneous grouping schemes (often based on birth weight categories), which may obscure the biological hierarchy in which gestational age is the primary factor and birth weight a derived characteristic [23]. A combined analytical approach—with simultaneous assessment of microbiota indicators (for example, markers of obligate taxa such as Lactobacillus and Bifidobacterium, and signals of opportunistic enterobacteria), as well as inflammatory and metabolic markers—may better reflect the axis of multisystem maturation distinguishing extremely preterm, late preterm, and term newborns [21,26]. Within such an integrative approach, serum magnesium represents a practical and clinically interpretable

marker that may demonstrate clear stepwise differences between gestational strata and correlate with microbiota maturation patterns, thereby serving as a useful indicator of biological maturity in observational studies of newborns [1,8,14].

OBJECTIVE:

To quantify between-group differences and association patterns between gestational age, gut microbiota indices, and key immuno-metabolic markers in newborns.

MATERIALS AND METHODS

Design: secondary analysis of aggregated clinical-laboratory and microbiological data (n=125). The analytical strategy and the choice of gestational age as the primary grouping criterion were defined a priori to keep the logic of the analysis transparent and to avoid data-driven changes. Although an initial spreadsheet structure used birth weight categories, we treated gestational age as the upstream biological determinant and birth weight as a derivative characteristic; therefore, all analyses are stratified by gestational age.

Groups: 26–31 weeks (n=56), 32–36 weeks (n=25), and ≥37 weeks (n=44).

Variables: gestational age (weeks), birth weight (g), birth length (cm); IL-1β and IL-10 (pg/mL), IgA (g/L), vitamin D (ng/mL), glucose (mmol/L), calcium (mmol/L), magnesium (mmol/L), potassium (mmol/L); and log-transformed microbiota indices (E. coli norm, UPE, Staph. coag. neg., Staph. epid./sap., Lactobacillus, Bifidobacterium).

Descriptive statistics are presented as Mean ± SD / Median (min–max). Group comparisons for key outcomes were performed using the Kruskal–Wallis test (df=2). Dwass–Steel–Critchlow–Fligner post-hoc testing was used for pairwise comparisons. Associations were evaluated using Spearman's rank correlation (n=125, two-tailed). Statistical significance threshold: $p<0.05$.

RESULTS AND DISCUSSION

Table 1. Cohort characteristics and basic laboratory markers by gestational-age group (Mean ± SD / Median (min–max))

Characteristic	26–31 w (n=56)	32–36 w (n=25)	≥37 w (n=44)
Gestational age, weeks	28.4 ± 1.95 / 28.0 (25.0–31.6)	34.1 ± 1.51 / 34.1 (32.0–36.4)	39.3 ± 1.32 / 39.1 (37.0–41.4)
Birth weight, g	1020 ± 334 / 946 (499–2220)	2091 ± 692 / 2000 (870–3530)	3133 ± 667 / 3065 (1440–4440)
Birth length, cm	33.5 ± 3.73 / 33.0 (22–43)	42.0 ± 3.74 / 41 (36–50)	49.6 ± 3.24 / 50.0 (37–54)
Glucose, mmol/L	2.77 ± 0.46 / 2.80 (2.01–4.10)	2.91 ± 0.28 / 3.00 (2.40–3.40)	3.02 ± 0.28 / 3.00 (2.10–3.80)
Calcium, mmol/L	1.99 ± 0.13 / 1.99 (1.78–2.40)	2.03 ± 0.11 / 2.00 (1.80–2.20)	2.09 ± 0.14 / 2.10 (1.85–2.40)
Potassium, mmol/L	4.12 ± 0.36 / 4.10 (3.40–5.00)	4.21 ± 0.47 / 4.10 (3.50–5.20)	4.60 ± 0.42 / 4.60 (3.80–5.40)
IL-10, pg/mL	11.3 ± 7.34 / 8.72 (1.33–31.1)	8.60 ± 6.08 / 6.80 (0.56–24.1)	9.04 ± 8.18 / 7.35 (0.36–28.2)

As expected, anthropometric characteristics (gestational age, birth weight, and birth length) differ clearly between the groups and reflect intrauterine growth and biological maturity. Electrolytes and basic biochemical parameters show general trends across gestational age groups; for example, potassium and calcium levels are slightly higher in term infants. In contrast, IL-10 shows marked individual variability and does not demonstrate a clear trend across groups

Table 2. Key immuno-metabolic markers by gestational-age group (Mean ± SD / Median (min–max))

Marker	26–31 w (n=56)	32–36 w (n=25)	≥37 w (n=44)	p (K-W)
IL-1β, pg/mL	7.12 ± 4.35 / 5.70 (1.60–24.4)	6.70 ± 5.58 / 6.77 (0.87–19.2)	4.53 ± 4.25 / 2.85 (0.24–18.4)	0.002
IgA, g/L	0.353 ± 0.812 / 0.058 (0.01–5.24)	0.393 ± 0.777 / 0.020 (0.01–2.80)	0.243 ± 0.753 / 0.020 (0.005–4.54)	0.002

Vitamin D, ng/mL	42.6 ± 29.5 / 31.2 (10.2–104)	51.1 ± 26.5 / 45.5 (12.0–100)	66.2 ± 28.1 / 61.8 (16.4–108)	<0.001
Magnesium, mmol/L	0.798 ± 0.069 / 0.795 (0.69–0.96)	0.874 ± 0.118 / 0.840 (0.70–1.20)	0.961 ± 0.098 / 0.960 (0.73–1.20)	<0.001

Vitamin D and magnesium increase with gestational age, while IL-1β decreases, supporting an integrated maturity gradient. Magnesium demonstrates the most consistent step-wise pattern across all three groups (post-hoc significant for each pair; see Table 5).

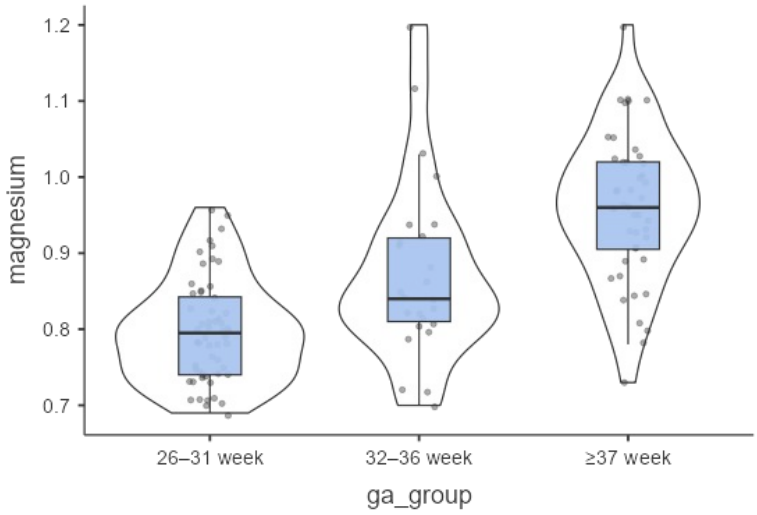

Figure 1. Distribution of serum magnesium concentration in newborns according to gestational age (boxplot with violin plot).

Figure 1 shows a progressive shift of serum magnesium to higher values with increasing gestational age; both the median and dispersion increase from 26–31 weeks to ≥37 weeks, consistent with the descriptive statistics.

Table 3. Gut microbiota indices (log) by gestational-age group (Mean ± SD / Median (min–max))

Index (log)	26–31 w (n=56)	32–36 w (n=25)	≥37 w (n=44)	p (K-W)
E. coli norm	1.23 ± 1.29 / 1.00 (0–6)	1.12 ± 1.20 / 1 (0–4)	0.57 ± 1.00 / 0 (0–3)	0.005
UPE	4.04 ± 1.82 / 4 (0–7)	3.32 ± 1.55 / 4 (1–7)	2.14 ± 1.30 / 2 (0–6)	<0.001
Staph. coag. neg.	0.39 ± 0.49 / 0	0.16 ± 0.37 / 0	0.02 ± 0.15 / 0	<0.001

	(0–1)	(0–1)	(0–1)	
Staph. epid./sap.	2.38 ± 1.52 / 2 (0–7)	1.76 ± 1.23 / 2 (0–6)	1.36 ± 0.84 / 1 (0–4)	<0.001
Lactobacillus	1.71 ± 2.11 / 1 (0–12)	3.28 ± 1.88 / 3 (0–7)	7.00 ± 11.1 / 6 (0–78)	<0.001
Bifidobacterium	1.41 ± 1.12 / 1 (0–5)	2.96 ± 3.45 / 1 (0–11)	7.52 ± 3.04 / 8 (0–11)	<0.001

Microbiota profiles show a clear maturity gradient: opportunistic enterobacterial flora (UPE) and staphylococcal indices decrease, while Lactobacillus and Bifidobacterium increase with increasing gestational age.

Gestational age as an integrative factor of biological maturity

Gestational age demonstrates statistically significant correlations with most studied parameters. As gestational age increases, IL-1β decreases ($\rho=-0.359$, $p<0.001$) and IgA decreases ($\rho=-0.324$, $p<0.001$), whereas vitamin D ($\rho=0.347$, $p<0.001$) and magnesium ($\rho=0.63$, $p<0.001$) increase. In parallel, Lactobacillus ($\rho=0.64$, $p<0.001$) and Bifidobacterium ($\rho=0.635$, $p<0.001$) increase, while UPE decreases ($\rho=-0.428$, $p<0.001$).

Inflammatory markers and microbiota

IL-1β shows negative correlations with Lactobacillus ($\rho=-0.206$, $p=0.021$) and Bifidobacterium ($\rho=-0.207$, $p=0.020$), suggesting that higher inflammatory activity is associated with lower abundance of obligate microbiota. UPE is inversely related to Lactobacillus ($\rho=-0.378$, $p<0.001$) and especially to Bifidobacterium ($\rho=-0.486$, $p<0.001$). A positive correlation between Lactobacillus and Bifidobacterium ($\rho=0.592$, $p<0.001$) reflects coordinated maturation of beneficial taxa.

Nutritional-metabolic status and microbiota

Vitamin D is positively correlated with Lactobacillus ($\rho=0.411$, $p<0.001$) and Bifidobacterium ($\rho=0.376$, $p<0.001$), and negatively correlated with E. coli

norm (ρ=−0.289, p=0.001) and UPE (ρ=−0.207, p=0.021). Similarly, magnesium is positively correlated with Lactobacillus (ρ=0.560, p<0.001) and Bifidobacterium (ρ=0.629, p<0.001), and negatively correlated with UPE (ρ=−0.318, p<0.001) and IL-1β (ρ=−0.229, p=0.010). These associations form a coherent profile in which a more favorable metabolic status corresponds to a microbiota profile dominated by obligate taxa and lower inflammatory activity.

IgA and IL-1β co-activation

A strong positive correlation between IgA and IL-1β (ρ=0.661, p<0.001) likely reflects coordinated immune activation in newborns with lower gestational age. IgA is negatively correlated with gestational age (ρ=−0.324, p<0.001), indicating higher IgA values in more premature infants within this cohort.

Summary of correlation analysis

Taken together, the correlation results show that gestational age is part of an integrated pattern of biological maturity and is associated with metabolic status (vitamin D, magnesium), immune activity (IL-1β, IgA), and gut microbiota composition (UPE, Lactobacillus, Bifidobacterium). These findings show associations only and do not indicate causal relationships; however, they describe a consistent and statistically supported maturation pattern.

Table 4. Kruskal–Wallis test summary (between-group differences)

Variable	χ^2	df	p
IL-1β	12.2	2	0.002
IgA	12.2	2	0.002
Vitamin D	17.8	2	<0.001
Magnesium	51.4	2	<0.001
E. coli norm (log)	10.5	2	0.005
UPE (log)	29.1	2	<0.001
Staph. epid./sap. (log)	14.0	2	<0.001

Lactobacillus (log)	53.2	2	<0.001
Bifidobacterium (log)	63.3	2	<0.001

All examined immunological, metabolic, and microbiological variables showed statistically significant differences between groups ($p \leq 0.005$), supporting gestational age as a primary factor of the combined phenotype.

Table 5. Pairwise comparisons (Dwass–Steel–Critchlow–Fligner), p-values

Variable	26–31 vs 32–36	26–31 vs ≥37	32–36 vs ≥37
IL-1β	0.524	<0.001	0.386
IgA	0.145	0.001	0.867
Vitamin D	0.222	<0.001	0.076
Magnesium	0.006	<0.001	0.002
E. coli norm (log)	0.949	0.004	0.079
UPE (log)	0.125	<0.001	0.004
Staph. epid./sap. (log)	0.153	<0.001	0.352
Lactobacillus (log)	<0.001	<0.001	<0.001
Bifidobacterium (log)	0.309	<0.001	<0.001

Post-hoc testing localized most differences to comparisons with the term group (≥37 weeks). Two indicators showed consistent step-wise differentiation across all three strata: magnesium and Lactobacillus (all pairwise $p \leq 0.006$).

Table 6. Selected key associations (Spearman ρ)

Pair	ρ	p
Gestational age vs Magnesium	+0.63	<0.001
Gestational age vs Lactobacillus (log)	+0.64	<0.001
Gestational age vs Bifidobacterium (log)	+0.635	<0.001
Gestational age vs UPE (log)	-0.428	<0.001
Gestational age vs IL-1β	-0.359	<0.001
IL-1β vs IgA	+0.661	<0.001
Vitamin D vs Lactobacillus (log)	+0.411	<0.001
Vitamin D vs Bifidobacterium (log)	+0.376	<0.001
Magnesium vs Bifidobacterium (log)	+0.629	<0.001

Magnesium vs UPE (log)	-0.318	<0.001

PRACTICAL IMPLICATIONS

In similar datasets, gestational age should be included as a key variable or stratification factor in analyses of microbiota and micronutrients. The present results suggest that serum magnesium and Lactobacillus (log) can be used as maturity-related indicators because they change step-wise across all gestational-age groups. This may be helpful for clinical risk assessment and for the interpretation of dysbiosis patterns in premature newborns.

LIMITATIONS

This study represents an observational secondary analysis based on aggregated data; therefore, causal inferences cannot be drawn. Potential clinical confounding factors, such as feeding strategy, antibiotic exposure, mode of delivery, and hospitalization-related factors, were not included in the analysis. Microbiota indices are presented in log units and may not fully reflect the absolute bacterial load.

CONCLUSION

Gestational age is closely associated with changes in the composition of the intestinal microbiota and immuno-metabolic parameters in newborns. As gestational age increases, a decrease in the level of opportunistic enterobacterial flora and IL-1β is observed, whereas concentrations of vitamin D, serum magnesium, as well as the abundance of Lactobacillus and Bifidobacterium, increase. Magnesium and Lactobacillus demonstrate pronounced stepwise differences across all three gestational age groups, which allows them to be considered informative indicators of neonatal maturity in this cohort.

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