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Association between Maternal Vitamin B-12 Deficiency and Early Neuro-developmental Biomarkers in Breastfed Neonates

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ABSTRACT

Vitamin B-12 plays a vital role in fetal brain development and early neurological function. Exclusively breastfed neonates are highly dependent on maternal B-12 stores and are at increased risk for early neurodevelopmental deficits in cases of maternal deficiency. However, evidence on this association during the neonatal period remains limited, especially in low-resource settings. **Objectives:** To assess the association between maternal vitamin B-12 deficiency and early neurodevelopmental outcomes in exclusively breastfed neonates within the first month of life. **Methods:** This cross-sectional analytical study was conducted on 91 mother-infant pairs. Maternal serum B-12 levels were measured postpartum, and infants were evaluated within the first 28 days using standardized neurodevelopmental assessments, including cognitive, motor, and language scores, as well as clinical markers like visual tracking, muscle tone, and developmental reflexes. Data were analyzed using SPSS, version 26.0 and associations were tested through independent t-tests and Chi-square analyses ($p<0.05$ considered significant). **Results:** Vitamin B-12 deficiency was found in 35.2% of mothers. Among the exclusively breastfed subgroup (n=46), no statistically significant differences were observed in cognitive (p=0.480), motor (p=0.473), or language scores (p=0.544) between neonates of B-12-deficient and B-12-sufficient mothers. Similarly, visual tracking deficits, abnormal muscle tone, and neurodevelopmental delay showed no significant associations with maternal B-12 status. **Conclusions:** Maternal vitamin B-12 deficiency did not demonstrate a measurable impact on early neurodevelopmental biomarkers in exclusively breastfed neonates during the first month of life. Larger longitudinal studies are needed to determine long-term consequences and guide maternal nutrition policies.

INTRODUCTION

Optimal maternal nutrition during pregnancy plays a critical role in fetal growth and neurological development [1]. Among the essential micronutrients, vitamin B-12 (cobalamin) is indispensable for neurogenesis, myelination, and the synthesis of neurotransmitters. It supports DNA synthesis and red blood cell formation, but more importantly, it influences brain structure and function through its role in methylation pathways. Maternal vitamin B-12 deficiency is widely prevalent in developing countries, with estimates ranging from 25% to over 70% in South Asia, including Pakistan, due to low intake of animal-sourced foods and poor dietary diversity [2, 3]. Neonates rely heavily on maternal B-12 stores acquired during gestation and through breast milk in early infancy. This makes exclusively breastfed infants particularly vulnerable to the consequences of maternal deficiency [4]. Clinical

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manifestations of B-12 deficiency in infants can range from subtle developmental delays to severe neurological impairments, including hypotonia, irritability, growth failure, and even regression of milestones if not addressed in time. Despite this, early signs are often nonspecific and may go unrecognized, particularly in the neonatal period [5]. The neonatal period, defined as the first 28 days of life, is a critical window for early brain development and synaptic organization. Nutritional insults during this stage can disrupt neurodevelopmental trajectories, and even mild deficiencies may lay the foundation for later impairments in cognition and language. As such, early identification of deficits, even if subclinical, may help predict long-term developmental outcomes and allow timely intervention [3, 6]. While the impact of severe maternal B-12 deficiency on long-term child development is well established, evidence remains inconclusive regarding its effect on early neurodevelopmental markers, especially within the first few weeks after birth [7]. This gap is even more pronounced in low-resource settings where B-12 deficiency often coexists with other nutritional and socioeconomic challenges. Moreover, most available studies focus on developmental outcomes at 6 to 12 months or later, with limited research addressing the neonatal stage, particularly among breastfed infants who depend exclusively on maternal nutritional reserves. By evaluating clinical biomarkers such as cognitive, motor, and language scores alongside neurosensory reflexes and muscle tone, this research aims to provide context-specific evidence that could guide early nutritional interventions in maternal and infant health.

This study aims to examine the association between maternal serum vitamin B-12 status and early neurodevelopmental outcomes in breastfed neonates within the first month of life.

METHODS

This cross-sectional analytical study was conducted at the Department of Pediatrics, Combined Military Hospital Rawalakot, affiliated with Poonch Medical College. Ethical approval was granted by the Institutional Review Committee under reference number 2445/SK132A N/CMH/Rawalakot. Data collection was conducted over six months, from October 2024 to March 2025. A minimum sample size of 91 mother-infant pairs was calculated using Open Epi software, based on an anticipated prevalence of vitamin B12 deficiency in pregnant women of approximately 30%, with a 95% confidence level and 10% margin of error. A non-probability consecutive sampling method was used to recruit eligible participants. Inclusion criteria included mothers aged 18–40 years delivering live-born neonates. Neonates aged ≤28 days at the time of developmental screening. Infants who were exclusively or predominantly breastfed. And provision of written informed consent by the mother or guardian. Exclusion criteria were neonates with major congenital anomalies or a history of birth asphyxia. Mothers with diagnosed chronic illnesses (e.g., diabetes, renal disease, autoimmune disorders). Neonates receiving postnatal vitamin B12 supplementation and neonates born before 34 weeks of gestation (late preterm and term infants were included). After informed consent, maternal and neonatal data were recorded using a structured proforma and supplemented with hospital records. Maternal data included age, parity, education, socioeconomic status, diet type, pregnancy supplement use, and mode of delivery. Maternal venous blood samples (5 ml) were collected within 48 hours postpartum. Serum vitamin B12 levels were measured using the Chemiluminescent Micro-Particle Immunoassay (CMIA) technique in the institutional biochemistry laboratory. The cutoff for deficiency was set at <200 pg/mL, consistent with international clinical guidelines, including the World Health Organization (WHO) [6] and regional studies conducted in South Asia [3], where this threshold is commonly used for identifying functionally deficient levels in pregnant and postpartum women. Neonatal data included gestational age, birth weight, Apgar score, head circumference, body length, and weight at the time of assessment. Neurodevelopment was evaluated using the Trivandrum Developmental Screening Chart (TDSC) and a structured neurological examination performed by a single trained pediatrician to ensure inter-rater consistency. The TDSC tool, validated for use in South Asia, measures cognitive, motor, and language domains, as well as visual tracking, auditory startle, muscle tone, and signs of global developmental delay. Since infants aged up to 28 days were eligible, age-standardization was addressed by assessing all milestones relative to the infant's exact postnatal age in days, and referencing the age-specific TDSC benchmarks for each developmental parameter. This ensured comparability across infants of different neonatal ages. Potential confounding variables such as maternal age, education, socioeconomic status, exclusive breastfeeding, and birth weight were pre-specified and assessed for association with maternal B12 status using Chi-square and t-tests. No statistically significant differences were observed between the B12-deficient and normal groups on these variables, suggesting that confounding was unlikely. Data were analyzed using IBM SPSS version 26.0. Descriptive statistics were presented as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables. Independent t-tests were used to compare mean neurodevelopmental scores across groups. Chi-square tests were applied for categorical comparisons (e.g., neurodevelopmental delay, abnormal tone). Normality of

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data was assessed using the Explore function, histogram inspection, and boxplots. Subgroup analysis was conducted on exclusively breastfed neonates. A p-value of <0.05 was considered statistically significant. To support clinical interpretation, mean differences and 95% confidence intervals (CIs) were reported. Laboratory analyses were conducted in duplicate, and standard internal quality control procedures were followed throughout.

RESULTS

The sample showed a near-equal distribution of maternal age, with 46 (50.5%) aged ≤25 years and 45 (49.5%) aged >25 years. Parity was similarly balanced, with 49.5% being primiparas and 50.5% multiparas. Education levels varied, with 24.2% of mothers being illiterate and 27.5% being graduates. A majority of participants belonged to the middle or high socioeconomic strata, and 54.9% delivered vaginally. Notably, 50.5% of mothers did not take supplements during pregnancy. Vitamin B12 deficiency (<200 pg/mL) was observed in 32 (35.2%) of the mothers. The mean maternal BMI was 22.82 ± 2.70 kg/m^2, indicating overall adequate nutritional status. The demographic and clinical profile of mothers is presented in Table 1.

Table 1: Maternal Demographic and Clinical Characteristics (n=91)

Variables	Category	Frequency (%)
Maternal Age	≤25 Years	46 (50.5%)
	>25 Years	45 (49.5%)
Parity	Primipara	45 (49.5%)
	Multipara	46 (50.5%)
Maternal Education	Illiterate	22 (24.2%)
	Primary	23 (25.3%)
	Secondary	21 (23.1%)
	Graduate	25 (27.5%)
Socioeconomic Status	Low	27 (29.7%)
	Middle	29 (31.9%)
	High	35 (38.5%)
Mode of Delivery	Normal/Vaginal	50 (54.9%)
	Cesarean	41 (45.1%)
Dietary Intake	Vegetarian	48 (52.7%)
	Non-Vegetarian	43 (47.3%)
Supplement Use in Pregnancy	Yes	45 (49.5%)
	No	46 (50.5%)
Serum Vitamin B-12 Status	Deficient	32 (35.2%)
	Normal	59 (64.8%)
Maternal BMI (kg/m^2)	Mean ± SD	22.82 ± 2.70

47 (51.6%) of neonates were full term, while 44 (48.4%) were preterm. The gender distribution was balanced. Exclusive breastfeeding was reported in 46 (50.5%) neonates. The mean age at assessment was 17.69 ± 5.60 days. Mean birth weight was 3056.66 ± 325.63 grams, and the Apgar score at 5 minutes was 8.45 ± 0.48. Head circumference, length, and weight were within normal neonatal ranges. Mean scores for cognition, motor, and language domains were 89.3 ± 10.7, 85.8 ± 9.0, and 82.8 ± 10.8, respectively. Visual tracking delays were noted in 48.4% of neonates, and auditory startle response was delayed in 46.2%. Muscle tone abnormalities were observed in 69.3% of neonates (hypertonia: 39.6%, hypotonia: 29.7%). Overall, 57.1% of neonates met the criteria for early neurodevelopmental delay, as shown in Table 2.

Table 2: Neonatal Characteristics of Study Participants and Early Neurodevelopmental Biomarkers (n=91)

Variables	Category / Statistic	Frequency (%) or Mean ± SD
Neonatal Characteristics of Study Participants		
Gestational Age	Preterm	44 (48.4%)
	Term	47 (51.6%)
Gender	Female	47 (51.6%)
	Male	44 (48.4%)
Exclusively Breastfed	Yes	46 (50.5%)
	No	45 (49.5%)
Neonatal Age (days)	Mean ± SD	17.69 ± 5.60
Birth Weight (grams)	Mean ± SD	3056.66 ± 325.63
Apgar Score at 5 min	Mean ± SD	8.45 ± 0.48
Head Circumference (cm)	Mean ± SD	33.85 ± 1.58
Length at Assessment (cm)	Mean ± SD	48.83 ± 2.14
Weight at Assessment (kg)	Mean ± SD	3.19 ± 0.42
Early Neurodevelopmental Biomarkers		
Cognitive Score	Mean ± SD	89.3 ± 10.7
Motor Score	Mean ± SD	85.8 ± 9.0
Language Score	Mean ± SD	82.8 ± 10.8
Visual Tracking	Normal	47 (51.6%)
	Delayed	44 (48.4%)
Auditory Startle Response	Normal	49 (53.8%)
	Delayed	42 (46.2%)
Muscle Tone	Normal	28 (30.8%)
	Hypotonia	27 (29.7%)
	Hypertonia	36 (39.6%)
Neurodevelopmental Delay	Yes	52 (57.1%)
	No	39 (42.9%)

To evaluate possible confounding effects, maternal and neonatal variables were compared between the B12-deficient and normal groups. No significant associations were found for maternal age, education, socioeconomic status, breastfeeding status, or birth weight (all p>0.05). These results indicate that maternal B12 status in this cohort was not confounded by the demographic or perinatal variables assessed, as shown in Table 3.

Table 3: Association of Confounding Variables with Maternal Vitamin B12 Status (n=91)

Variables	Category	Deficient n (%)	Normal n (%)	p-value
Maternal Age	>25 Years	14 (43.8%)	31 (52.5%)	0.423
	≤25 Years	18 (56.3%)	28 (47.5%)	

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Maternal Education	Graduate	10 (31.3%)	15 (25.4%)	0.880
	Illiterate	7 (21.9%)	15 (25.4%)	
	Primary	7 (21.9%)	16 (27.1%)	
Socioeconomic Status	Secondary	8 (25.0%)	13 (22.0%)	0.230
	High	16 (50.0%)	19 (32.2%)	
	Middle	9 (28.1%)	20 (33.9%)	
	Low	7 (21.9%)	20 (33.9%)	
Exclusively Breastfed	Yes	14 (43.8%)	32 (54.2%)	0.339
	No	18 (56.3%)	27 (45.8%)	
Birth Weight (grams)	Mean ± SD	3062.63 ± 292.37	3053.42 ± 344.70	0.898

The mean cognitive score was 90.78 ± 9.60 in the deficient group vs. 88.43 ± 11.22 in the normal group (mean difference = +2.34, 95% CI: -7.01 to 2.32, p=0.320). Motor and language scores also showed no statistically significant differences (p=0.637 and p=0.403, respectively). Neurodevelopmental delay occurred in 59.4% of deficient vs. 55.9% of normal neonates (p=0.751). These results suggest no significant relationship between maternal B12 status and early neurodevelopmental performance, as shown in Table 4.

Table 4: Association of Maternal B12 Status with Early Neurodevelopmental Outcomes (n=91)

Outcome Variables	Deficient (n=32)	Normal (n=59)	Mean Difference (95% CI)	p-value
Cognitive Score (Mean ± SD)	90.78 ± 9.60	88.43 ± 11.22	+2.34 (-7.01 to 2.32)	0.320
Motor Score (Mean ± SD)	86.41 ± 8.73	85.47 ± 9.17	+0.94 (-4.87 to 3.00)	0.637
Language Score (Mean ± SD)	81.52 ± 9.61	83.52 ± 11.41	-1.99 (-6.71 to 2.73)	0.403
Neuro-developmental Delay	19 (59.4%)	33 (55.9%)	–	0.751

Among exclusively breastfed neonates (n=46), no statistically significant differences were found in cognitive, motor, or language scores between the B12-deficient and normal groups. Visual tracking deficits, abnormal tone, and neurodevelopmental delay were more frequent in the B12-deficient group, but these trends did not reach statistical significance (all p>0.05), as shown in Table 5.

Table 5: Neurodevelopmental Outcomes by B12 Status in Exclusively Breastfed Neonates (n=46)

Outcome Variables	B12 Deficient (n=14)	B12 Normal (n=32)	p-value
Cognitive Score (Mean ± SD)	90.35 ± 11.81	87.55 ± 12.47	0.480
Motor Score (Mean ± SD)	88.86 ± 9.06	86.79 ± 8.84	0.473
Language Score (Mean ± SD)	81.49 ± 11.88	83.70 ± 11.03	0.544
Visual Tracking Deficit	6 (42.9%)	11 (34.4%)	0.584
Abnormal Muscle Tone†	9 (64.3%)	21 (65.7%)	0.768
Neurodevelopmental Delay	9 (64.3%)	17 (53.1%)	0.482

†Abnormal tone includes both hypotonia and hypertonia

DISCUSSION

This study investigated the association between maternal vitamin B-12 deficiency and early neurodevelopmental biomarkers in breastfed neonates. Among 91 participants, 35.2% of mothers were vitamin B-12 deficient, yet no statistically significant associations were found between maternal B-12 status and neonatal cognitive, motor, or language scores, nor with neurodevelopmental delays. Even in the subgroup of exclusively breastfed neonates, neurodevelopmental outcomes did not differ significantly by maternal B-12 levels. Additionally, no significant associations were observed between maternal B-12 deficiency and perinatal confounding factors such as maternal age, education, or birth weight. These findings suggest that maternal B-12 status during late pregnancy may not independently predict neurodevelopmental outcomes within the first month of life. This aligns and contrasts with existing literature in several ways. In other studies, our study found no significant difference in cognitive, motor, or language scores based on B-12 status. This is consistent with Cruz-Rodríguez *et al.* and Keskin et al. who noted that infant neurodevelopment at 6 weeks and 3 months was not significantly influenced by maternal B-12 alone, especially in the absence of folate or iron co-deficiencies [8, 7]. The RCT by Solvik *et al.* provided high-dose maternal B-12 during pregnancy and lactation but found no significant improvement in Bayley-III scores at 6 and 12 months of age, even though maternal and infant B-12 levels improved markedly [9]. Wirthensohn *et al.* also reported that short-term developmental outcomes in neonates did not significantly differ by maternal B-12 intake, especially in middle-income populations with borderline but not severe deficiency [10]. Curremt findings were also consistent with Kumar *et al.* who concluded that routine B-12 supplementation in pregnancy may improve hematological and biochemical markers, but does not consistently lead to measurable cognitive gains in early infancy [5]. It is important to consider that B-12-related neurodevelopmental deficits often manifest after 6 to 12 months of age. As noted by Bjørkevoll *et al.* delayed onset of symptoms is common, particularly in mild or subclinical deficiency states [11]. In our cohort, visual tracking and auditory startle responses were not significantly related to B-12 status. Similarly, Siddiqua *et al.* found no relationship between maternal B-12 and sensory-motor integration at birth in a large South Indian sample [12]. A Czech cohort study found that while B-12 intake during pregnancy predicted language development and IQ at age 8, early infancy assessments were poor predictors, again supporting our finding of non-significance in the neonatal period [13]. Our study's lack of association between exclusive breastfeeding and neurodevelopmental delay

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mirrors findings by Ljungblad *et al.* who noted that B-12 content in breastmilk is often insufficient to influence early milestones unless maternal deficiency is severe [14]. Because our assessments were conducted within the first 28 days of life, it is plausible that this early timing limited our ability to detect subtle developmental differences that might emerge later in infancy. This limitation is supported by another longitudinal study, which found that early infancy assessments are poor predictors of longer-term neurocognitive function [15]. Another consideration is the potential for subclinical or subtle neurodevelopmental impairments to go undetected using the TDSC screening tool. Although TDSC is validated for early developmental delay, its sensitivity for detecting mild neurocognitive deficits or emerging executive function delays in neonates may be limited. As such, it is possible that early B-12-related effects existed but were not captured due to the tool's screening nature rather than diagnostic depth. Ulak *et al.* observed that while long-term cognitive development was related to prenatal B-12 status, no difference was seen in anthropometry or milestones at birth or 1 month, aligning directly with our data [15]. Reischl-Hajiabadi et al. assessed infants at 4 months using the Denver II scale and found only mild differences in motor and language development in B-12-deficient mothers, none of which were statistically significant [16]. St-Cyr emphasizes that deficiency thresholds and timing matter; deficiency in early pregnancy or pre-conception is more predictive of outcomes than late third-trimester values, which our study captured [17]. Bakken *et al.* noted that early postpartum B-12 status (≤1 month postpartum) had no significant association with development at 1 month, but stronger associations appeared at 6–12 months [18]. A study by Garzone and Zanella in Guatemala concluded that neurodevelopmental markers at 2 weeks were weakly associated with any nutritional biomarker, reinforcing the idea that postnatal age at assessment limits sensitivity [19]. Studies argued for longitudinal neurodevelopmental surveillance when studying micronutrient deficiencies, as effects often take time to manifest in expressive language and problem-solving domains [20].

CONCLUSIONS

Despite a high prevalence of maternal vitamin B-12 deficiency (35.2%) in our cohort, no significant impact was found on early neonatal neurodevelopmental outcomes such as cognitive, motor, or language scores. These results suggest that neurodevelopmental assessment in the first month of life may not be sensitive enough to detect subtle effects of prenatal B-12 deficiency. In light of global and regional evidence, our findings highlight the importance of early gestational or pre-conception B-12 correction rather than late third-trimester interventions, longer follow-up periods into infancy or childhood to capture latent developmental impacts, and the need to integrate B-12 with other nutritional interventions, particularly in resource-limited or vegetarian populations. Future research should focus on multi-nutrient interventions, time-sensitive supplementation, and neurocognitive tracking beyond 6–12 months to more accurately assess the full impact of maternal B-12 deficiency on child development.

Authors Contribution

Conceptualization: JI
Methodology: JI, AH, MUS, SI, MAJ, FR
Formal analysis: JI, AH, MUS, SI
Writing review and editing: JI, AH, MUS, SI, MAJ, FR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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