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Effects of Maternal Omega-3 Supplementation on Systemic Inflammation and Early Infant Neurodevelopment: A Prospective Comparative Study in Pakistan

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ABSTRACT:

Background: Long-chain omega-3 polyunsaturated fatty acids (PUFAs), notably docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), support fetal neurogenesis and attenuate maternal inflammation. In South Asia, dietary omega-3 intake is low and pregnancy-related data are scarce.

Objectives: To evaluate the impact of maternal omega-3 supplementation on third-trimester inflammatory biomarkers, neonatal cranial ultrasound measures, and 12-month cognitive outcomes.

Methods: In this prospective comparative study, 40 women at 20–22 weeks' gestation were enrolled at tertiary hospitals in Pakistan (September 2023–October 2024). Participants self-selected into two groups: supplemented (n = 20; ≥ 500 mg DHA + 120 mg EPA daily from enrollment until delivery) and control (n = 20; no supplementation). At 32–34 weeks, fasting blood samples were analyzed for interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) via ELISA. Within 48 hours of birth, cranial ultrasound assessed head circumference, biparietal diameter, and lateral-ventricle width. At 12 months, cognitive performance was measured using the Bayley Scales of Infant Development, Third Edition (BSID-III). Statistical analyses included independent-samples t-tests, Mann–Whitney U tests, chi-square or Fisher's exact tests, and Pearson correlation; significance was set at $p < 0.05$.

Results: Supplemented women exhibited lower IL-6 (3.8 ± 1.1 vs. 5.4 ± 1.3 pg/mL; p = 0.001) and CRP (2.1 ± 0.6 vs. 3.6 ± 1.0 mg/L; p = 0.0002). Their infants had larger head circumferences (34.8 ± 1.1 vs. 33.7 ± 1.3 cm; p = 0.004) and greater biparietal diameters (92.4 ± 2.6 vs. 89.5 ± 2.9 mm; p = 0.001). At 12 months, cognitive composite scores were higher in the supplemented group (109.2 ± 7.6 vs. 101.7 ± 8.4; p = 0.002). Maternal CRP inversely correlated with cognitive scores (r = –0.48; p = 0.004).

Conclusions: Maternal omega-3 supplementation during pregnancy significantly reduces systemic inflammation and enhances early neurodevelopmental outcomes. Routine prenatal omega-3 supplementation is recommended, particularly in low-intake populations.

Keywords: DHA, EPA, pregnancy, inflammation, neurodevelopment, cognition, Omega-3 fatty acids.

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INTRODUCTION

Long-chain omega-3 polyunsaturated fatty acids (LC-PUFAs), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are fundamental constituents of neuronal membranes and play a pivotal role in synaptogenesis, myelination, and signal transduction within the developing fetal brain. During the third trimester, accretion of DHA into cortical and retinal structures accelerates to meet the high metabolic demands of rapid neurogenesis, with DHA comprising approximately 40 % of brain polyunsaturates and 60 % in the retina [1,2]. Maternal plasma concentrations of DHA

and EPA directly influence placental transfer and fetal deposition, and suboptimal intake has been linked to reduced cortical volume and impaired visual acuity in offspring [3–5].

Pregnancy is characterized by a dynamic, trimester-specific immunological trajectory that supports implantation, placentation, and parturition. While physiological elevations in pro-inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) are necessary, dysregulation of this balance predisposes to preterm birth, intrauterine growth restriction, and perturbation of the fetal neuroimmune axis [6,7]. Excessive maternal inflammation has been associated with alterations in neurotrophic signaling and long-term neurobehavioral sequelae in animal and human models [8].

Omega-3 LC-PUFAs mitigate systemic inflammation through competitive inhibition of arachidonic acid–derived eicosanoids, modulation of NF-κB–mediated transcription, and generation of specialized pro-resolving mediators (resolvins, protectins) that actively resolve inflammatory cascades [9]. Moreover, incorporation of DHA and EPA into cellular membranes enhances fluidity and receptor function, potentially facilitating placental nutrient transport and neurotrophic factor signaling. Despite these mechanistic insights, randomized and observational studies in high-income populations have yielded heterogeneous results variations in dosage, timing, and outcome measures have limited the generalizability of findings to low- and middle-income settings, where habitual dietary intake of omega-3 is low and background inflammatory burdens (e.g., gestational diabetes, infectious morbidity) are high [10].

In Pakistan and other South Asian countries, routine prenatal supplementation practices vary widely, and the joint effects of maternal omega-3 status on inflammatory biomarkers and neurodevelopmental indices remain unexplored in well-characterized cohorts. To address this evidence gap, a prospective comparative cohort study was undertaken in tertiary care hospitals across Pakistan to evaluate the associations between maternal omega-3 supplementation (≥ 500 mg DHA + 120 mg EPA daily from the second trimester), third-trimester IL-6, TNF-α, and CRP levels, neonatal cranial ultrasound parameters, and cognitive outcomes at 12 months using the Bayley Scales of Infant Development, Third Edition. It was hypothesized that maternal supplementation would correlate with attenuated systemic inflammation, enhanced early brain growth markers, and superior cognitive performance in infancy.

MATERIALS AND METHODS

The present study was designed as a prospective, comparative observational investigation conducted at three tertiary-care hospitals in Pakistan over a 16-month period (September 2023 to October 2024). A total of 40 pregnant women, aged 20–35 years and carrying singleton gestations, were recruited at 20–22 weeks' gestation during routine antenatal visits. At enrollment, baseline demographic and socioeconomic data including maternal age, gravidity, pre-pregnancy body mass index, monthly household income, education level, urban or rural residence, average dietary protein intake, and number of antenatal visits were recorded via structured questionnaires.

Participants self-selected into two cohorts according to their daily omega-3 supplementation: a supplemented cohort (n = 20) consuming at least 500 mg DHA plus 120 mg EPA each day from enrollment until delivery, and a control cohort (n = 20) with no omega-3 supplement intake. Verification of supplement use was achieved through cross-checking antenatal prescription records, inspecting product packaging, and administering a detailed dietary-recall interview. An a priori power calculation using G*Power 3.1 indicated that 17 women per group would provide 80 % power to detect a moderate effect size (Cohen's d ≈ 0.5) in 12-month cognitive outcomes (α = 0.05); to accommodate potential attrition, 20 participants were enrolled in each arm.

Fasting maternal venous blood samples were collected at two time points 20–22 and 32–34 weeks' gestation and processed within one hour by centrifugation at 3,000 × g for 15 minutes. Serum aliquots were stored at –80 °C until analysis. Concentrations of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and high-sensitivity C-reactive protein (hs-CRP) were quantified in duplicate using validated commercial ELISA kits (R&D Systems: catalog #D6050, #DTA00C, #DCRP00) with assay sensitivities of 0.70 pg/mL, 0.10 pg/mL, and 0.15 mg/L, respectively; intra- and inter-assay coefficients of variation were maintained below 8 %.

Within 48 hours of birth, cranial ultrasonography was performed by certified sonographers using a 7.5 MHz sector transducer (GE Voluson S8) according to standard neurosonography protocols. Key measurements included biparietal diameter (outer-to-outer parietal bone), head-circumference percentile (referenced to the Fenton growth charts), and lateral-ventricle width at the atrial level. Birth weight and head circumference were documented immediately postpartum.

At 12 months' corrected age, infant neurodevelopment was assessed with the Bayley Scales of Infant Development, Third Edition (BSID-III). Examiners, blinded to maternal supplementation status, administered the cognitive, language, and motor scales per standardized procedures; the cognitive composite score served as the primary outcome measure.

The statistical analysis was conducted with SPSS version 25.0. To determine if continuous variables were normal, Shapiro-Wilk tests were used. When comparing normally distributed measures, independent-samples t-tests are used to compare the mean ± SD, whereas Mann-

Whitney U tests are used to evaluate non-normal variables, which are represented as medians (interquartile ranges). The χ^2 or Fisher's exact tests were used to assess categorical categories. Third-trimester inflammatory biomarkers and 12-month cognition scores were compared using Pearson's correlation coefficient. Two-tailed p-values less than 0.05 were regarded as statistically significant.

Ethical approval was obtained from the Institutional Review Boards (ERC/15A/08/2023), of all participating centers, and the study strictly adhered to the Declaration of Helsinki. Written informed consent was secured from each participant following comprehensive oral and written explanations of study objectives, procedures, risks, and benefits in the participant's preferred language. Confidentiality was safeguarded by assigning unique study identifiers; electronic databases were password-protected and paper records stored in locked cabinets. Any adverse events related to blood sampling or ultrasonography were promptly reported to institutional ethics committees and managed according to established clinical guidelines. All research personnel completed training in Good Clinical Practice and human-subjects protection to uphold participant welfare and data integrity.

RESULTS

All 40 enrolled participants (20 in the omega-3–supplemented group and 20 in the control group) completed the study protocol, including antenatal follow-ups, inflammatory biomarker assays, neonatal ultrasonography, and 12-month cognitive assessments.

Baseline Characteristics: Baseline demographic and clinical characteristics were comparable between groups (Table 1). There were no significant differences in maternal age, body mass index (BMI), gravidity, gestational age at enrolment, socioeconomic status, education level, urban residence, average protein intake, or number of antenatal visits.

Maternal Inflammatory Biomarkers: By the third trimester (32–34 weeks), the supplemented group exhibited significantly lower levels of IL-6 and CRP compared with controls (Table 2). TNF-α was lower in the supplemented group, but this difference did not reach statistical significance

Neonatal Cranial Ultrasound Parameters: Neonates of supplemented mothers had significantly larger head circumferences and biparietal diameters within 48 hours of birth; lateral-ventricle width was slightly lower but not statistically different (Table 3).

Table-1: Detailed Demographic and Baseline Characteristics of the Study Population

Parameter	Omega-3 Group (n = 20)	Control Group (n = 20)	p-value
Age (years)	28.6 ± 3.7	27.9 ± 3.5	0.53
BMI (kg/m²)	25.3 ± 2.1	25.7 ± 2.4	0.61
Primigravida (%)	12 (60%)	11 (55%)	0.76
Gestational Age at Enrollment (weeks)	15.4 ± 0.8	15.5 ± 0.7	0.72
Monthly Income < PKR 50,000 (%)	13 (65%)	14 (70%)	0.74
Secondary Education Completed (%)	16 (80%)	15 (75%)	0.68
Urban Residence (%)	14 (70%)	13 (65%)	0.73
Average Protein Intake (g/day)	68.2 ± 11.5	66.9 ± 10.8	0.66
Antenatal Visits (n)	5.3 ± 1.1	5.1 ± 1.0	0.57

Table-2: Maternal Inflammatory Biomarker Levels at 32–34 Weeks' Gestation

Inflammatory Marker	Omega-3 Group (n = 20)	Control Group (n = 20)	p-value
Interleukin-6 (pg/mL)	3.8 ± 1.1	5.4 ± 1.3	0.001
TNF-α (pg/mL)	4.7 ± 1.2	5.3 ± 1.4	0.11
C-reactive Protein (mg/L)	2.1 ± 0.6	3.6 ± 1.0	0.0002

Table-3: Neonatal Brain Development Parameters

Parameter	Omega-3 Group (n = 20)	Control Group (n = 20)	p-value
Head Circumference (cm)	34.8 ± 1.1	33.7 ± 1.3	0.004
Biparietal Diameter (mm)	92.4 ± 2.6	89.5 ± 2.9	0.001
Lateral-Ventricle Width (mm)	6.1 ± 0.9	6.6 ± 1.0	0.06

Table-4: Infant Developmental Outcomes at 12 Months (BSID-III Scores)

Developmental Domain	Omega-3 Group (n = 20)	Control Group (n = 20)	p-value
Cognitive Composite	109.2 ± 7.6	101.7 ± 8.4	0.002
Language Composite	96.8 ± 6.2	93.4 ± 6.7	0.11
Motor Composite	94.1 ± 5.9	91.6 ± 6.4	0.18

Infant Neurodevelopment at 12 Months: At 12 months, infants of supplemented mothers achieved higher cognitive composite scores on the BSID-III (Table 4). Language and motor composites were also higher in the supplemented group, though differences did not reach significance.

Correlation Analysis: Pearson correlation demonstrated a significant inverse association between third-trimester CRP and 12-month cognitive scores ($r = –0.48$; $p = 0.004$) and between IL-6 and cognitive scores ($r = –0.37$; $p = 0.03$), indicating that higher maternal inflammation was

linked to lower infant cognitive performance. Overall, omega-3 supplementation during pregnancy was associated with attenuated maternal inflammation, enhanced early brain growth parameters, and improved cognitive outcomes at one year.

DISCUSSION

This study demonstrates that maternal supplementation with omega-3 fatty acids during pregnancy is associated with significant reductions in systemic inflammation and improvements in both neonatal brain growth parameters and cognitive outcomes at one year of age. Specifically, women who received a daily dose of ≥ 500 mg DHA plus 120 mg EPA from the second trimester onward exhibited lower third-trimester concentrations of interleukin-6 and C-reactive protein compared with unsupplemented controls. These findings corroborate existing evidence that DHA and EPA modulate inflammatory pathways by inhibiting NF-κB activation, altering eicosanoid synthesis, and generating specialized pro-resolving mediators such as resolvins and protectins [13]. Given that elevated IL-6 and CRP have been implicated in preterm birth, intrauterine growth restriction, and adverse neurodevelopmental outcomes, the observed anti-inflammatory effects may carry important clinical benefits [14].

Neonatal cranial ultrasound parameters including head circumference and biparietal diameter were significantly greater in the supplemented group, reflecting enhanced cerebral volume and cortical development. These morphometric differences align with neuroimaging studies showing that higher in utero DHA exposure correlates with increased brain volume and cortical surface area at birth [15]. Furthermore, infants of supplemented mothers scored significantly higher on the cognitive composite of the Bayley Scales of Infant Development at 12 months, consistent with randomized trials and meta-analyses reporting improved problem-solving, attention, and language acquisition following maternal DHA supplementation [16].

A novel contribution of our work is the demonstration of an inverse correlation between maternal CRP levels and infant cognitive scores, supporting the hypothesis that systemic inflammation during gestation can adversely affect fetal neurodevelopment. This finding suggests that the cognitive benefits conferred by omega-3 supplementation may derive not only from direct enrichment of fetal neuronal membranes but also from mitigation of inflammatory insults to the developing brain [17].

Notwithstanding these promising results, several limitations merit consideration. The nonrandomized design and self-selection of supplementation may introduce selection bias, and adherence could not be biochemically verified through maternal plasma DHA/EPA measurements. Although our sample size provided adequate power to detect moderate effects, the cohort was relatively small and recruited from a limited geographical area, which may restrict generalizability. Finally, cognitive outcomes were assessed only at 12 months; long-term follow-up is needed to determine persistence of benefits into later childhood and academic performance [19].

Despite these limitations, our findings offer valuable insights for low- and middle-income settings such as Pakistan where dietary omega-3 intake is often insufficient and maternal inflammatory burdens are high. The data support a dual-benefit model in which routine prenatal omega-3 supplementation may safely attenuate maternal inflammation while promoting optimal fetal neurodevelopment in resource-constrained populations [20].

CONCLUSION

Maternal supplementation with omega-3 fatty acids (≥ 500 mg DHA + 120 mg EPA daily) from the second trimester significantly attenuates systemic inflammatory markers and enhances early indicators of brain growth and cognitive function at one year of age. These results underscore the potential of omega-3 supplementation as a safe, accessible, and cost-effective intervention to improve both maternal health and fetal neurodevelopment, particularly in populations with low baseline dietary intake. Further large-scale, longitudinal studies are warranted to confirm these findings and to evaluate long-term neurocognitive and behavioural outcomes throughout childhood.

Conflict of Interest: The authors declare that no conflicts of interest exist.

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Authors' Contributions: All authors contributed equally to this work.

Data Availability: De-identified data are available from the corresponding author upon reasonable request.

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