**A mixed lipid emulsion containing fish oil and its effect on electrophysiological brain maturation in extremely low birth weight infants: A secondary analysis of a randomized clinical trial**

Christoph Binder, MD1; Vito Giordano, PhD1; Margarita Thanhaeuser, MD1; Alexandra Kreissl, PhD1; Mercedes Huber-Dangl, MD1; Nicholas Longford, PhD2; Nadja Haiden, MD1; Angelika Berger, MD1; Andreas Repa, MD1;Katrin Klebermass-Schrehof, MD1

1 Department of Pediatrics and Adolescent Medicine, Division of Neonatology, Pediatric Intensive Care Medicine and Neuropediatrics; Medical University of Vienna, Austria

2 Section of Neonatal Medicine, Department of Medicine; Imperial College London, Chelsea and Westminster Campus, London, United Kingdom

**Corresponding author:**

Andreas Repa, MD

Department of Pediatrics and Adolescent Medicine

Medical University of Vienna

Waehringer Guertel 18-20,

1090 Vienna, Austria

Tel: +43-1-40400-32320, Fax: +43-1-40400-32380

andreas.repa@meduniwien.ac.at

**Word count: 2334**

**Key Points**

**Question:**

Does parenteral nutrition using a mixed lipid emulsion composed of soybean oil, medium chain triglycerides, olive oil and fish oil differently affect electrophysiological brain maturation compared to soybean oil-based lipid emulsion?

**Findings:**

Analysis of serial amplitude-integrated EEG measurements from 121 extremely low birth weight (< 1000 grams) infants (mixed lipid emulsion: n=63; soybean oil: n=58) revealed a significant acceleration of electrophysiological brain maturation using the mixed lipid emulsion.

**Meaning:**

Electrophysiological brain maturation was accelerated in extremely low birth weight infants using a mixed lipid emulsion that contains fish oil, which may indicate a neurodevelopmental benefit.

**ABSTRACT**

**Importance:** Docosahexaenoic acid comprises 40% of total brain fatty acids and is considered an important functional and structural component. Preterm infants accumulate large deficits after birth. A new mixed lipid emulsion that contains fish oil provides docosahexaenoic acid comparable to *in utero* amounts. Effects on brain maturation in preterm infants are unknown.

**Objective:** To examine the effect of parenteral nutrition using a mixed lipid emulsion that contains fish oil on electrophysiological brain maturation in extremely low birth weight infants.

**Design:** Pre-specified secondary outcome analysis of a randomized controlled trial (06/2012 – 10/2015) on parenteral nutrition associated cholestasis. Electrophysiological brain maturation was assessed bi-weekly by amplitude-integrated EEG.

**Setting:** A level IV neonatal care unit (University Children’s Hospital Vienna).

**Participants:** Participants included 121 (intervention: n=63; control: n=58) out of 230 extremely low birth weight (< 1000 grams) infants. Reasons for non-eligibility were non-availability of records (n=85), intraventricular hemorrhage (n=11), sedative drugs at measurement (n=4) and cystic periventricular leucomalacia (n=2).

**Intervention:** A lipid emulsion composed of soybean oil, medium chain triglycerides, olive oil and fish oil (intervention) or a soybean oil-based lipid emulsion (control).

**Main outcome and measures:** Electrophysiological brain maturation (background activity, sleep-wake cycling and brain maturational scores) assessed by amplitude-integrated EEG.

**Results:** A total of 317 aEEG measurements were analyzed (intervention: n=165; control: n=152). Demographic characteristics did not differ between the two groups. Starting from 28 weeks postmenstrual age, infants receiving the intervention displayed a significantly higher percentage of continuous background activity. Total maturational scores and individual scores for continuity, cycling and bandwidth were significantly higher and maximum brain maturational scores were reached by two weeks earlier in the intervention group (36.4 weeks, 35.4 - 37.5) compared to the control group (38.4 weeks, 37.1 -42.4) (median postmenstrual age, interquartile range; *P*<.001).

**Conclusions and Relevance:** Electrophysiological brain maturation was accelerated in preterm infants using a mixed parenteral lipid emulsion that contains fish oil. An impact on long-term neurodevelopment seems possible.

**Trial registration:** ClinicalTrials.gov Identifier: NCT01585935

# INTRODUCTION

Infants with extremely low birth weight (ELBW, birth weight <1000 grams) are at high risk of adverse neurological outcome.1 Current neuroprotective strategies comprise the use of antenatal steroids, magnesium sulfate and caffeine.2 Optimized nutrition positively supports brain maturation and neurocognitive development of ELBW infants.3,4 Here, omega (-3 long-chain polyunsaturated fatty acids (LC-PUFA) are important for normal brain development.5-7 The (-3 LC-PUFA docosahexaenoic acid (DHA) comprises 40% of total brain fatty acids and is considered a main structural and functional component.5,6 *In utero*, high amounts of DHA are transferred to the fetus in the last trimester to meet the demands of rapid brain growth.8,9 In preterm infants, DHA supply from enteral nutrition falls short of fetal demands,8 and their capacity to synthetize DHA from (-3 precursor fatty acids is low.10 ELBW infants are therefore at particular risk due to initially low enteral intake10 and absence of DHA in parenteral soybean oil-based lipid emulsions (LE) – which are currently the only approved LE for parenteral nutrition (PN) of preterm infants in the US.11

A new mixed LE composed of soybean oil, medium chain triglycerides, olive oil and fish oil (SMOF-LE)12 provides DHA and its immediate precursor eicosapentaenoic acid (EPA).13 In a recent randomized clinical trial12, we assigned ELBW infants to receive either SMOF-LE or a soybean oil-based LE for PN to analyze its preventive effect against parenteral nutrition associated cholestasis and found no difference. As yet, it is still unknown whether increasing DHA supply by PN using SMOF-LE affects brain maturation in these infants. In this study, we therefore analyzed amplitude-integrated electroencephalography (aEEG) recordings of study participants. Our aim was to investigate the effect of SMOF-LE compared to the soybean oil-based LE on electrophysiological brain maturation in ELBW infants.

**METHODS**

**Study design**

This study is a pre-specified secondary outcome analysis of a double-blind randomized controlled trial12 (ClinicalTrials.gov NCT01585935) conducted at the University Children’s Hospital Vienna (Medical University of Vienna, Austria) from June 2012 to October 2015. The primary outcome or any other relevant neonatal morbidity did not differ significantly.12 The study design was previously described in more detail.12 In summary, ELBW infants without conditions associated with cholestasis were eligible. After consent, participants were randomized and stratified (sex and birth weight <750 versus ≥750 grams) within their first five days of life. The intervention was blinded for patients and observers, including the analysis of data in this study. Participants received a mixed LE (SMOF-LE) composed of 30% soybean oil, 20% medium chain triglycerides, 25% olive oil and 15% fish oil (SMOFlipid 20%; Fresenius Kabi, Bad Homburg, Germany) or a soybean oil-based LE (Intralipid 20%; Fresenius Kabi, Bad Homburg, Germany).14 SMOF-LE contains (wt/wt) 2.2% DHA, 2.4% EPA and 200 mg/L α-tocopherol, while the soybean oil-based LE is devoid of DHA and EPA and contains 38 mg/L α-tocopherol.14 Both groups received parenteral vitamins (2 ml/kg Soluvit; 4 ml/kg Vitalipid N Infant, provides 2.6 mg/kg α-tocopherol; Fresenius Kabi, Bad Homburg, Germany) until fortification of human milk feedings. Enteral nutrition was commenced using own mother´s milk or human donor milk. If donor milk was used, infants were switched to preterm formula after 32 weeks of postmenstrual age (PMA). Milk feedings were fortified using a fat free fortifier at 100 ml/kg (Aptamil FMS; Danone, Paris, France). Parenteral nutrition was stopped at 140-160 ml/kg/day of enteral nutrition.

## Analysis of brain maturation by aEEG

Amplitude-integrated EEG of study participants was recorded bi-weekly as part of clinical routine using a single channel aEEG (CFM 6000; Natus Medical Incorporated, San Carlos, CA).15 For analysis of brain maturation in this study, infants with severe intraventricular hemorrhage (IVH grade III/IV) and cystic periventricular leucomalacia (PVL)16 were excluded post-hoc. Brain maturation was assessed by classification of background patterns (BP) and sleep wake cycles (SWC) according to Hellstrom-Westas et al17 and calculation of maturational scores according to Burdjalov et al18. Analysis was performed by two independent investigators (K.K-S. and C.B.). Inter-rater agreement was assessed by Cohen´s Kappa. Any discordance was dissolved by discussion and consensus. Only aEEG sequences recorded without sedative or anti-epileptic drugs19 with a duration over 90 minutes and impedance below 20 kΩ were used.20 For analysis of BP according to Hellstrom-Westas et al17 (Table 2), aEEG traces were subdivided in 10 minute periods, rated as continuous, discontinuous, burst suppression, low voltage or flat trace 17 and reported as percentage distribution. Sleep-wake cycles of individual aEEG records (Table 2) were classified as absent, mature or immature17. Results are reported according to the PMA period (weeks + days) at assessment: 24+0 to 27+6, 28+0 to 29+6, 30+0 to 31+6, 32+0 to 33+6, 34+0 to 35+6 and 36+0 to 41+6.

Brain maturational scores according to Burdjalov et al.18 were calculated from aEEG traces based on continuity (0-2), cycling (0-5), lower border amplitude (0-2) and bandwidth (0-4) and reported according to the PMA period at assessment (Table 3). For better visualization, total maturational scores (0-13) were individually plotted with trajectories (Figure 2). To assess the time of full brain maturation, the PMA as individual participants reached their maximum score (13 points) was plotted (Figure 3). For participants who did not reach the maximum score, the estimated PMA of maximum maturation was plotted as approximated by linear extrapolation.21

## Baseline characteristics

A full course of antenatal steroids was defined as two doses of betamethasone. Surfactant (Curosurf; Chiesi, Parma, Italy) was administered prophylactically to infants born <28 weeks PMA or otherwise therapeutically if surfactant deficiency was suspected. Anthropometry was performed by the attending nurses and z-scores were calculated using growth curves by Fenton et al.22 Supply with parenteral DHA, EPA and α-tocopherol was calculated. Necrotizing enterocolitis (NEC) was diagnosed clinically (Bell´s stage ≥ IIa)23 or after exploratory surgery. Bronchopulmonary dysplasia (BPD) was defined as supplementary oxygen after 36+0 weeks PMA. Retinopathy of prematurity was diagnosed by direct ophthalmoscopy. IVH and cystic PVL24 were diagnosed by cerebral ultrasound performed every 7-14 days.

## Statistics

Data are expressed as median and interquartile range (IQR) or mean and standard deviation (SD). Statistical testing was specified post hoc. T-Test or Mann-Whitney U-Test were used to compare continuous data depending on normality as tested using the Kolmogorov-Smirnov test. The chi-square test was used to compare categorical data and frequency distribution of SWC between groups. Kruskal-Wallis rank test was used to compare BP and maturational scores. Inter-rater agreement of aEEG analysts was assessed by Cohen´s Kappa. A *P*-value of <.05 was considered statistically significant.

# RESULTS

## Screening

A total of 230 ELBW infants were randomly assigned (Figure 1) and 223 infants were available for analysis of the primary outcome.12 For assessment of electrophysiological brain maturation, aEEG records from 138 of 223 infants were available. After excluding infants with severe IVH or cystic PVL and those with sedative/anti-epileptic drugs at all aEEG measurements, 121 infants (SMOF-LE: n=63; soybean oil-based LE: n=58) with 317 usable aEEG traces (excluded due to short duration/sedative drugs: n=12) remained for analysis (SMOF-LE: n=165; soybean oil-based LE: n= 152).

## Baseline characteristics

Demographic characteristics and neonatal morbidities of infants eligible for analysis of aEEG did not differ significantly between the groups (Table 1). Infants of the SMOF-LE group received significantly more parenteral DHA, EPA and α-tocopherol due to the nature of the intervention.

## Amplitude-integrated EEG measurements

The postmenstrual age at analyses reached from 24 to 41 weeks PMA. The duration of recordings (median, IQR) did not differ significantly between groups (SMOF-LE: 180 minutes (150, 260); soybean oil-based LE: 180 minutes (140, 240); *P*=.30). Inter-rater agreement for aEEG analysts was high (Cohen´s kappa: 0.93 for BP, 0.90 for SWC and 0.90 for maturational scores).

### Pattern analysis according to Hellstrom-Westas

Analysis of aEEG pattern17 is shown in Table 2. Starting from 28 weeks PMA, the percentage of continuous BP was significantly higher in infants who received SMOF-LE. Mature SWC were the dominant pattern after 33 weeks PMA in all infants and the percentage of mature SWC did not differ significantly between groups.

### Maturational scores according to Bjurdalov

The scores for cycling and bandwidth were significantly higher in infants receiving SMOF-LE, starting from 28 weeks PMA (Table 3). Also, lower border amplitude scores were significantly higher from 28 to 31 weeks and continuity from 28 to 33 weeks PMA. The summative total maturational score was significantly higher from 28 to 41 weeks PMA.

Individual maturational score trajectories revealed accelerated electrophysiological maturation in infants receiving SMOF-LE (Figure 2). As shown in Figure 3, maximum electrophysiological maturation (median, IQR) was reached at 36.4 weeks (35.4, 37.5) PMA in infants receiving SMOF-LE compared to 38.4 weeks (37.1, 42.4) in infants receiving soybean oil-based LE, a statistically significant difference of two weeks (*P*<.001).

# DISCUSSION

Our study of serial aEEG measurements showed accelerated electrophysiological brain maturation in ELBW infants receiving a mixed lipid emulsion that contains fish oil. Infants receiving SMOF-LE reached significantly higher scores for aEEG activity, cycling, continuity and bandwidth, and presented with significantly more continuous background activity - both sensitive indicators of brain maturation18,25 and predictors of neurodevelopment.26,27

The aim of nourishing the preterm infant is to achieve growth and body composition similar to a healthy fetus,28 coupled with satisfactory neurodevelopment. In this context, optimal nutrition is of great importance, and adequate supply with DHA is highly relevant for an undisturbed cerebral development.4,9 After preterm birth, DHA supply exclusively relies on enteral nutrition, but falls short of fetal accretion rates.10 Endogenous synthesis of DHA only insufficiently covers fetal demands.11 Parenteral nutrition using soybean oil based LE provides high loads of essential fatty acids (linoleic and linolenic acid), but not DHA. Thus, ELBW infants who rely on PN in their first weeks of life accumulate the largest DHA deficits.9,10 To support cerebral development adequately, it thus seems appropriate to supply DHA with PN in amounts comparable to the fetus. Infants who received SMOF-LE in our study (Table 2) were provided with DHA comparable to *in utero* accretion (45 mg/kg/d)10.

Several *in vitro* studies have provided direct evidence for the important beneficial effects of DHA on neurite growth and synaptic function.29-33 Electrocortical activity - as it was measured by aEEG in our study - is the aggregate of post-synaptic potentials15 and thus correlates with the synaptic number and activity. In this context, improved supply with DHA in our trial might have enhanced cerebral neurite growth and/or synaptogenesis which translated into accelerated electrophysiological brain maturation. In support of this hypothesis Helland et al.34 have reported on an association of DHA levels and the maturity of EEG in term infants.

Besides DHA, there are further components of SMOF-LE with a potential impact on cerebral development. Eicosapentaenoic acid, which is also provided by SMOF-LE (Table 1) in similar amounts, was shown to promote myelination in newborn rats - even better than DHA.35 Improved white matter connectivity was shown to increase EEG coherence36 - which corresponds to increased continuous background activity in aEEG. Thus, improved myelination may also explain some of our findings, but only magnetic resonance imaging would clarify such an effect - which was not part of our study. We therefore cannot directly report on myelination and could only speculate whether supply with EPA was significant for our findings. It is however a shortcoming of every clinical trial investigating -3 LC-PUFA supplementation, that effects of DHA and EPA are hard to separate - as both are provided using fish oil.37

Finally, SMOF-LE contains five times more α-tocopherol (Table 1) compared to a soybean oil-based LE.33,38 Cerebral α-tocopherol protects neuronal membranes from oxidative damage39 and is involved in processes related to neuronal plasticity.40 In a recent study from the US, it was shown that parenteral α-tocopherol supply to ELBW infants was below recommendations.41 Considering the supply with total parenteral α-tocopherol in our study, both groups had a sufficient supply with parenteral α-tocopherol (Table 1; recommended range 2.8-3.5 mg/kg/d, maximum 7 mg/kg/d42) with infants receiving SMOF-LE even exceeding current recommendations. Pharmacological α-tocopherol supplementation (5-30 mg/kg/d) was linked to sepsis and NEC.43 We and other colleagues44 did not find any significant influence of SMOF-LE on sepsis or NEC,45 but caregivers should be aware of the high supply of α-tocopherol using SMOF-LE together with parenteral multivitamin preparations.42 Whether such a supraphysiological supply of α-tocopherol contributed to electrophysiological brain maturation in our study is speculative, but eventually cannot be excluded.

Neurodevelopmental safety of new interventions is of eminent importance in preterm infants and must be proven by adequate studies.46 Acceleration of electrophysiological brain maturation using SMOF-LE may suggest safety or even benefit, but currently there are no reports on neurodevelopment using SMOF-LE. Several studies have shown an association of early changes in aEEG pattern – as seen in our study - and favorable neurodevelopmental outcomes.17,26 Thus accelerated electrophysiological brain maturation may point out to improved neurodevelopment. This interpretation might be supported by studies that showed a neurodevelopmental benefit of DHA enriched preterm formula in subsets of preterm infants.47 In these studies, DHA supply (25-59 mg/kg/d) was quite similar to our study, though parenteral and enteral DHA substitution cannot be directly compared.48 Along these lines, a retrospective observational study by Tam et al. showed that higher levels of DHA were associated with better neurodevelopment and improved microstructural brain maturation.49 By now, we can only speculate on the significance of our findings concerning neurodevelopment or structural changes of the developing brain. Further trials are therefore necessary to draw firm conclusions on a possible neurodevelopmental influence and imaging studies on structural brain changes would be of major interest.

It is a weakness of our study that analysis of brain maturation by aEEG was only a secondary outcome and loss to follow up was relatively high, introducing a possibility for bias. Nevertheless, the study population was randomized, investigators were blinded and the baseline characteristics of infants analyzed remained well balanced. Furthermore, the remaining sample size of 121 preterm infants with 317 aEEG records still represents a large cohort and differences were statistically significant across almost all parameters of aEEG, making chance rather unlikely.

# Conclusion

Our study showed that electrophysiological brain maturation in ELBW infants was significantly accelerated using SMOF-LE, which may predict a relevant impact on neurodevelopment. Neurodevelopmental long-term follow up in these infants is therefore of high interest.

# References

1. Mercier CE, Dunn MS, Ferrelli KR, Howard DB, Soll RF, Vermont Oxford Network EIF-USG. Neurodevelopmental outcome of extremely low birth weight infants from the Vermont Oxford network: 1998-2003. *Neonatology.* 2010;97(4):329-338.

2. Lea CL, Smith-Collins A, Luyt K. Protecting the premature brain: current evidence-based strategies for minimising perinatal brain injury in preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2017;102(2):F176-F182.

3. Keunen K, van Elburg RM, van Bel F, Benders MJ. Impact of nutrition on brain development and its neuroprotective implications following preterm birth. *Pediatr Res.* 2015;77(1-2):148-155.

4. Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. *Am J Clin Nutr.* 2007;85(2):614S-620S.

5. Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Extrauterine fatty acid accretion in infant brain: implications for fatty acid requirements. *Early Hum Dev.* 1980;4(2):131-138.

6. Scott BL, Bazan NG. Membrane docosahexaenoate is supplied to the developing brain and retina by the liver. *Proc Natl Acad Sci U S A.* 1989;86(8):2903-2907.

7. Coti Bertrand P, O'Kusky JR, Innis SM. Maternal dietary (n-3) fatty acid deficiency alters neurogenesis in the embryonic rat brain. *J Nutr.* 2006;136(6):1570-1575.

8. Kuipers RS, Luxwolda MF, Offringa PJ, Boersma ER, Dijck-Brouwer DA, Muskiet FA. Fetal intrauterine whole body linoleic, arachidonic and docosahexaenoic acid contents and accretion rates. *Prostaglandins Leukot Essent Fatty Acids.* 2012;86(1-2):13-20.

9. Harris WS, Baack ML. Beyond building better brains: bridging the docosahexaenoic acid (DHA) gap of prematurity. *J Perinatol.* 2015;35(1):1-7.

10. Lapillonne A, Jensen CL. Reevaluation of the DHA requirement for the premature infant. *Prostaglandins Leukot Essent Fatty Acids.* 2009;81(2-3):143-150.

11. Vanek VW, Seidner DL, Allen P, et al. A.S.P.E.N. position paper: Clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract.* 2012;27(2):150-192.

12. Repa A, Binder C, Thanhaeuser M, et al. A Mixed Lipid Emulsion for Prevention of Parenteral Nutrition Associated Cholestasis in Extremely Low Birth Weight Infants: A Randomized Clinical Trial. *J Pediatr.* 2018;194:87-93 e81.

13. Fell GL, Nandivada P, Gura KM, Puder M. Intravenous Lipid Emulsions in Parenteral Nutrition. *Adv Nutr.* 2015;6(5):600-610.

14. Rayyan M, Devlieger H, Jochum F, Allegaert K. Short-term use of parenteral nutrition with a lipid emulsion containing a mixture of soybean oil, olive oil, medium-chain triglycerides, and fish oil: a randomized double-blind study in preterm infants. *JPEN J Parenter Enteral Nutr.* 2012;36(1 Suppl):81S-94S.

15. Maynard DE. EEG processing by the Cerebral Function Monitor (CFM). *Ann Anesthesiol Fr.* 1979;20(3):170-174.

16. Olischar M, Klebermass K, Waldhoer T, Pollak A, Weninger M. Background patterns and sleep-wake cycles on amplitude-integrated electroencephalography in preterms younger than 30 weeks gestational age with peri-/intraventricular haemorrhage. *Acta Paediatr.* 2007;96(12):1743-1750.

17. Hellstrom-Westas L, Rosen I. Continuous brain-function monitoring: state of the art in clinical practice. *Semin Fetal Neonatal Med.* 2006;11(6):503-511.

18. Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. *Pediatrics.* 2003;112(4):855-861.

19. Bell AH, Greisen G, Pryds O. Comparison of the effects of phenobarbitone and morphine administration on EEG activity in preterm babies. *Acta Paediatr.* 1993;82(1):35-39.

20. Olischar M, Klebermass K, Kuhle S, et al. Reference values for amplitude-integrated electroencephalographic activity in preterm infants younger than 30 weeks' gestational age. *Pediatrics.* 2004;113(1 Pt 1):e61-66.

21. Hazewinkel ME. *Encyclopaedia of Mathematics (set), Springer.* ISBN: 978-1-55608-010-4; 2001.

22. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr.* 2013;13:59.

23. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am.* 1986;33(1):179-201.

24. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res.* 1992;49(1):1-6.

25. Thorngate L, Foreman SW, Thomas KA. Quantification of neonatal amplitude-integrated EEG patterns. *Early Hum Dev.* 2013;89(12):931-937.

26. Bruns N, Dransfeld F, Huning B, et al. Comparison of two common aEEG classifications for the prediction of neurodevelopmental outcome in preterm infants. *Eur J Pediatr.* 2017;176(2):163-171.

27. Fogtmann EP, Plomgaard AM, Greisen G, Gluud C. Prognostic Accuracy of Electroencephalograms in Preterm Infants: A Systematic Review. *Pediatrics.* 2017;139(2).

28. Hay WW, Jr. Aggressive Nutrition of the Preterm Infant. *Curr Pediatr Rep.* 2013;1(4).

29. Brenna JT, Diau GY. The influence of dietary docosahexaenoic acid and arachidonic acid on central nervous system polyunsaturated fatty acid composition. *Prostaglandins Leukot Essent Fatty Acids.* 2007;77(5-6):247-250.

30. Cao D, Kevala K, Kim J, et al. Docosahexaenoic acid promotes hippocampal neuronal development and synaptic function. *J Neurochem.* 2009;111(2):510-521.

31. Tanaka K, Farooqui AA, Siddiqi NJ, Alhomida AS, Ong WY. Effects of docosahexaenoic Acid on neurotransmission. *Biomol Ther (Seoul).* 2012;20(2):152-157.

32. Calderon F, Kim HY. Docosahexaenoic acid promotes neurite growth in hippocampal neurons. *J Neurochem.* 2004;90(4):979-988.

33. McDougall M, Choi J, Magnusson K, Truong L, Tanguay R, Traber MG. Chronic vitamin E deficiency impairs cognitive function in adult zebrafish via dysregulation of brain lipids and energy metabolism. *Free Radic Biol Med.* 2017;112:308-317.

34. Helland IB, Saugstad OD, Smith L, et al. Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. *Pediatrics.* 2001;108(5):E82.

35. Salvati S, Natali F, Attorri L, et al. Eicosapentaenoic acid stimulates the expression of myelin proteins in rat brain. *J Neurosci Res.* 2008;86(4):776-784.

36. Kurth S, Achermann P, Rusterholz T, Lebourgeois MK. Development of Brain EEG Connectivity across Early Childhood: Does Sleep Play a Role? *Brain Sci.* 2013;3(4):1445-1460.

37. Kidd PM. Omega-3 DHA and EPA for cognition, behavior, and mood: clinical findings and structural-functional synergies with cell membrane phospholipids. *Altern Med Rev.* 2007;12(3):207-227.

38. Mangialasche F, Xu W, Kivipelto M, et al. Tocopherols and tocotrienols plasma levels are associated with cognitive impairment. *Neurobiol Aging.* 2012;33(10):2282-2290.

39. Fukui K, Omoi NO, Hayasaka T, et al. Cognitive impairment of rats caused by oxidative stress and aging, and its prevention by vitamin E. *Ann N Y Acad Sci.* 2002;959:275-284.

40. Ambrogini P, Betti M, Galati C, et al. alpha-Tocopherol and Hippocampal Neural Plasticity in Physiological and Pathological Conditions. *Int J Mol Sci.* 2016;17(12).

41. Porcelli PJ, Weaver RG, Jr. The influence of early postnatal nutrition on retinopathy of prematurity in extremely low birth weight infants. *Early Hum Dev.* 2010;86(6):391-396.

42. Bronsky J, Campoy C, Braegger C, nutrition EEECwgopp. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Vitamins. *Clin Nutr.* 2018.

43. Johnson L, Bowen FW, Jr., Abbasi S, et al. Relationship of prolonged pharmacologic serum levels of vitamin E to incidence of sepsis and necrotizing enterocolitis in infants with birth weight 1,500 grams or less. *Pediatrics.* 1985;75(4):619-638.

44. Kapoor V, Glover R, Malviya MN. Alternative lipid emulsions versus pure soy oil based lipid emulsions for parenterally fed preterm infants. *Cochrane Database Syst Rev.* 2015(12):CD009172.

45. Repa A, Binder C, Thanhaeuser M, et al. A Mixed Lipid Emulsion for Prevention of Parenteral Nutrition Associated Cholestasis in Extremely Low Birth Weight Infants: A Randomized Clinical Trial. *J Pediatr.* 2017.

46. Robertson AF. Reflections on errors in neonatology III. The "experienced" years, 1970 to 2000. *J Perinatol.* 2003;23(3):240-249.

47. Wang Q, Cui Q, Yan C. The Effect of Supplementation of Long-Chain Polyunsaturated Fatty Acids During Lactation on Neurodevelopmental Outcomes of Preterm Infant From Infancy to School Age: A Systematic Review and Meta-analysis. *Pediatr Neurol.* 2016;59:54-61 e51.

48. Nilsson AK, Lofqvist C, Najm S, et al. Influence of Human Milk and Parenteral Lipid Emulsions on Serum Fatty Acid Profiles in Extremely Preterm Infants. *JPEN J Parenter Enteral Nutr.* 2018.

49. Tam EW, Chau V, Barkovich AJ, et al. Early postnatal docosahexaenoic acid levels and improved preterm brain development. *Pediatr Res.* 2016;79(5):723-730.