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Randomized controlled trial of brain specific fatty acid supplementation in pregnant women increases brain volumes on MRI scans of their newborn infants

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ABSTRACT

Docosahexaenoic acid (DHA) and arachidonic acid (ArA) are essential brain specific fatty acids (BSFA) for mammalian central nervous system development. Human brains have accelerated growth with significant increase in cerebral content of ArA and DHA during the last trimester of pregnancy and first postnatal months. This randomized double blind placebo controlled single centre trial assessed the impact of BSFA supplementation in pregnancy on newborn infants' brain volumes. Eighty six infants born to study mothers had brain magnetic resonance imaging (MRI) scans soon after birth. Total and regional brain volumes were analyzed and related to maternal supplementation group. Males born to the BSFA supplemented mothers had significantly larger total brain volumes, total gray matter, corpus callosum and cortical volumes when compared to the placebo group. This is the first study to show maternal BSFA supplementation enhances newborn infants' brain size and suggests differential sex sensitivity of fetal brains to pregnancy BSFA status.

List of Abbreviations

ADHD	attention deficit hyperactive disorder
ASD	autistic spectrum disorder
ArA	arachidonic acid
BSFA	brain specific fatty acids
DHA	docosahexaenoic acid
DMR	differentially methylated regions
EFA	essential fatty acids
GDM	gestational diabetes mellitus
LBW	low birthweight
MUFA	monounsaturated fatty acids
LCPUFA	long chain polyunsaturated fatty acids
MRI	magnetic resonance imaging
PET	pre-eclamptic toxaemia

1. Introduction

The omega n-3 and n-6 long chain fatty acid series are important components of tissue lipids, especially cell membrane phospholipids [1,2]. Arachidonic acid (ArA), an omega-6 fatty acid (FA), is present in all biological membranes and represents approximately 5–15% of the total FAs in most tissue phospholipids [3] but can be as high as 30–40% in placental and prenatal T-lymphocyte inner membranes [4]. However, docosahexaenoic acid (DHA), an n-3 long chain polyunsaturated fatty acid (LCPUFA), has a more specific tissue distribution. Although only a small percentage of the fatty acids in most tissue lipids, DHA is present at very high levels in the retina, cerebral cortex, testis, and sperm [5]. These high levels are found consistently in mammalian species, despite disparities in dietary intakes of n-3 FAs [6,7]. This specific and consistent tissue distribution provided the first evidence of the importance of DHA in these tissues.

Essential fatty acids (EFAs) are required for cell function and deficiency causes irreversible changes in brain development and function [8,9]. The synthesis of ArA and DHA from parent EFAs during high body growth velocities is often insufficient and while ArA is readily available in typical Western diets [10,11], DHA is relatively limited [12]. For both ArA and DHA, the placenta returns the precursors to the

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mother whilst it bio-magnifies the proportion of ArA and DHA for the fetal circulation. This process of bio-magnification results in negligible amounts of DHA precursors in human fetal liver and blood making any fetal conversion academic [13]. Consistent with the process of bio-magnification, the proportions of ArA and DHA are lower in a pregnant versus a non-pregnant woman's circulation. Therefore, increasing the intake of DHA during pregnancy can enhance maternal DHA status, potentially benefiting the fetus. Connor et al. [14] reported that pregnant women who consumed regular amounts of sardines or brain specific FAs (BS) FAs increased their plasma DHA levels and transferred more n-3 PUFA to their fetuses.

As stated above, n-3 and n-6 LCPUFAs are suggested to be critical for infant and childhood brain development with data indicating that an adequate supply of DHA particularly during pregnancy, lactation and childhood is essential for normal neurodevelopment [15,16]. Although several studies have reported positive associations between blood DHA levels and improved cognitive and visual function in preterm, term infants and healthy children, the results have been inconsistent [17–21]. A comprehensive review by Brenna in 2016 [22] reported that there are only 3 published studies specifically showing the importance of ArA in human infants neurocognition showing that feeds with the highest ArA had the greatest impact on neurodevelopment. Therefore, potential long-term benefits of early LCPUFA supplementation need further evaluation. To date, no studies have investigated the relationship between maternal prenatal LCPUFA supplementation and neonatal brain volumes as assessed by MRI. This study assesses that relationship.

2. Patients and methods

This is a double-blind randomized placebo controlled study as previously described by Ogundipe et al. [23].

Null hypothesis: Infants born to women supplemented with BSFA in early pregnancy will not have higher total and/or gray matter brain volumes on MRI scans compared to controls.

The aim of the study was to determine whether maternal BSFA supplementation in pregnancy is related to the total and regional brain volumes of their newborn infants. The intervention was supplementation with 2 capsules daily of either “DHA-enriched formula” or “placebo (high oleic acid sunflower seed oil)”. Each active supplement capsule contained 300 mg of DHA, 42 mg of eicosapentaenoic acid (EPA) and 8.4 mg of ArA, and placebo 721 mg of oleic acid; (Vifor Pharma Switzerland). Ogundipe's group [23] previously showed that maternal lipid status in early pregnancy was a strong predictor of pregnancy outcomes. Women who delivered preterm babies irrespective of their risk group had lower levels of DHA and ArA and higher mono-unsaturated fatty acid (MUFA)/oleic acid levels than those with normal pregnancy outcomes. As described previously in that paper, it was for this reason that we used 600 mg DHA for 12 weeks. An independent third party, CLINIPACE AG, undertook the blinding and labelling of the supplements and interim data monitoring. Women were recruited from routine antenatal booking clinics at Chelsea and Westminster Hospital London, UK.

Three hundred pregnant women were recruited from the 1st July 2010 over a two - year period. Their infants were enrolled after further consent to undergo MRI brain scans. Normal healthy women as well as high-risk pregnant women were approached. The high-risk groups included women predisposed to the birth of a low birthweight (LBW) infant, such as, smokers, previous LBW baby, history of pre-eclamptic toxaemia (PET) and nulliparity, a risk factor for PET which predisposes to LBW births and a group of those with risk factors for developing/or with gestational or type II diabetes mellitus. See List of abbreviation for maternal risk group selection.

2.1. Ethics and consent to participate

Written consent was obtained from all participants prior to entry to both parts of the study. Written consent was sought from all participants and further written consent was obtained from the parents and guardians for the participation of their infants for MRI scans and also for use of chloral hydrate sedation or not for the scans.

The City and East London Research Ethics Committee granted ethical approval: No: 07/H0704 99. The study was indemnified by Chelsea and Westminster NHS Foundation Trust, Research and Development department and was registered as a randomized controlled trial- ISRCTN24068733.

2.2. Recruitment

Mothers: had their socio-demographic, antenatal and postnatal course and lipid profile were documented.

Exclusions: were if non-English speaking who decline use of an interpreter, non-resident in London and/or unable to attend the follow up appointments, known fish allergy and known chronic illness e.g. HIV Infants:

Neonatal outcomes recorded included their sociodemography, perinatal outcomes including sex, gestation length, birthweight and head circumference. Cord blood was taken at delivery to determine the fetal lipid profile. The infant brain MRI scans were planned to be undertaken within 4 weeks of their birth.

2.3. Magnetic resonance imaging (MRI)

Brain MRI was performed at a neonatal MRI centre on a 3-T Philips Achieva MRI system (Best, The Netherlands), using an eight-channel phased-array head coil. Parents were offered the choice of having their infants sedated with chloral hydrate for the examination and gave consent or not to use a sedative. Pulse oximetry, temperature and heart rate were monitored throughout the scan, and ear protection was used including silicone-based putty earplugs (President Putty; Coltene/Whaledent, Mahwah, NJ), and neonatal earmuffs (Natus MiniMuffs; Natus Medical, San Carlos, CA). Imaging protocol included a 3D magnetization-prepared rapid acquisition gradient echo (parameters: TR 17 ms; TE 4.6 ms; flip angle 13°; voxel size 0.82 × 0.82 × 0.5), a turbo spin echo T2-weighted (parameters: TR 15,731 ms; TE 160 ms; flip angle 90°; voxel size 0.86 × 0.86 × 1), and a single-shot echo planar diffusion MRI (dMRI) sequence acquired in 32 non-collinear directions (b-value 750 s/mm^2, in-plane resolution 1.75 mm × 1.75 mm; slice thickness 2 mm; TR 9000 ms; TE 49 ms). MR images were analyzed by a paediatric neuroradiologist. Where congenital or acquired brain lesions of clinical significance were detected parents and the family general practitioner were notified about the findings and appropriate follow-up was arranged. MR images were analyzed offline using tools implemented in FMRIB's Software Library (FSL) (www.fmrib.ox.ac.uk/fsl/fslwiki) described by Smith et al. [24] and Image Registration Toolkit by Rueckert et al. [25]. For each infant, following brain extraction and correction for bias field inhomogeneities of T2-weighted images, binary cortical, hippocampal, lentiform, thalamic, corpus callosum, whole white matter and whole brain masks were derived with automated tissue segmentation driven by age-specific priors reported by Makropoulos et al. [26]. Absolute volumes were determined and adjusted for gestational age (GA) at scan (Fig. 1).

2.4. Power calculation

To detect a 15% difference in total brain volume [27] on MRI brain scans of infants born to BSFA supplemented versus placebo control mothers with a power of 0.9 and significance level of 0.05 with two-sample equal variances, the study required at least 14 subjects per arm.