Review article

Prenatal PUFA undernutrition and risk of adult psychiatric disorders

Islam A

Abstract:
The developing fetus requires significant amounts of poly unsaturated fatty acids (PUFAs/ FAs) to maintain its normal cellular growth and integrity. Suboptimal intrauterine conditions, including poor PUFAs nutrition, during critical periods of growth may lead to lifelong changes in the body's organs and tissues, thus providing a physiological basis for adult-onset disease. However, the Developmental Origins of Health and Disease (DOHaD) model provide a structure to assess the effect of early nutrition and growth on long-term health. Epidemiological statistics shows that when pregnant mothers experienced malnutrition or famine (e.g. the Dutch Hunger Winter of 1944-1945 and the Chinese famine of 1959-1961), the risk of developing metabolic and psychiatric disease in their children increased. The theory of DOHaD is well referenced in the understanding of adult metabolic diseases, but less so in the field of psychiatric disorders. As PUFAs play critical roles in brain development, considerable effort has been taken in elucidating their function in the pathogenesis of neuropsychiatric disorders.

Key words: PUFAs, FABP, prenatal undernutrition, psychiatric disorder.

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Introduction:

PUFAs are critical structural component of mammalian cell and must be obtained from food. Likewise, PUFAs are precursors of eicosanoids, which exert hormonal and immunological activity. The properties of the n-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have met with considerable interest in the last few years. In particular, the vascular protective effects of n-3 PUFAs are well documented. EPA und DHA are known to affect the lipid profile, vascular tone and blood coagulation[1]. Owing to their anti-inflammatory effects, another possibility is to positively affect inflammatory disorders such as rheumatoid arthritis[2]. In addition to these properties, increasing evidence suggests that n-3 PUFAs also play a central role in brain development and the proper functioning of central nervous system. Together with n-6 PUFAs, they are not only involved in the development and maturation of neuronal structures, but are essential throughout the entire life span for maintaining normal brain and nervous system function[3].

In prenatal stage, the fetus receives its essential nutrition from maternal circulation through the placenta, a selective barrier for nutrients including PUFAs which is critically important for fetus. Transplacental exchange of nutrients and waste products between mother and fetus is essential for fetal development and survival. Following on the seminal interpretation of DOHaD hypothesis[4], maternal hormonal and nutrient environment has been systematically implicated in effects on the developing fetus that ultimately influence susceptibility to a wide range of metabolic, neurodevelopmental, and psychiatric diseases in adulthood[5,6]. In this review, the impact of maternal dietary undernutrition of n-3 and n-6 PUFAs on fetal development focusing on adult psychosis was discussed from recent known evidence.

PUFAs in cell biology

Mammalian cells utilize three main types of fatty acids (FAs): saturated FAs, which do not contain any double bonds; monounsaturated FAs (MUFAs), which contain a single double bond; and polyunsaturated FAs (PUFAs), which contain multiple double bonds. Among them PUFAs are important biological constituents having metabolic, structural, and signaling roles. The developing fetus requires substantial amounts of FAs to support rapid cellular growth and activity and among them; the n-3 (also termed as ω-3) and n-6 (ω-6) PUFAs are crucial[7]. The most biologically important n-3 and n-6 PUFAs are eicosapentaenoic acid (EPA; 20:5n-

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3), docosahexaenoic acid (DHA; 22:6n-3), dihomo gamma linolenic acid (20:3n-6), and arachidonic acid (AA; 20:4n-6)[7]. While these PUFAs are metabolic derivatives of the essential fatty acids, α-linolenic acid (ALA), and linoleic acid (LA) most readily obtained from the diet.

Unlike plants, mammals are not able to synthesize the parent PUFA compounds (n-6; LA and n-3; ALA). Therefore, they must be obtained through the consumption of vegetables contained PUFA. In contrast, mammals are capable to synthesize the long-chain derivatives of these PUFAs, in particular AA, EPA and DHA from LA and ALA in a multistage conversion process in the endoplasmic reticulum of liver cells[8,9]. Because the placental desaturase activity/fetal enzyme activity is limited in utero, the fetus depends on placental PUFAs transfer[10,11]. High amounts of DHA are incorporated into brain/retinal membranes and modulate membrane fluidity and permeability, improve photoreceptor differentiation and may impact on enzyme activity, respectively[11]. Intrauterine requirements for essential FAs (derivatives of n-6 and n-3) during the last trimester of pregnancy through to the early weeks of life have been estimated to be 400 and 50 mg/kg/day for n-6 and n-3 PUFAs, respectively[12]. Structurally, AA and DHA are key components of neuronal membranes, making up 15–20% of the brain's dry mass and more than 30% of the retina[13]. In early life, both n-3 and n-6 PUFAs are critical for supporting brain growth and maturation. AA is crucial to brain growth, and mild deficiencies are associated with low birth weight and reduced head circumference[14]. It also plays a key role in the cellular processes underlying learning and memory[15]. DHA is particularly concentrated in highly active membranes such as synapses and photoreceptors, and adequate supplies are essential for normal visual and cognitive development[16,17]. Pre-formed PUFAs are found naturally in breast milk, and although some controlled studies have shown advantages to both visual and cognitive development from their addition to infant formula[18].

Mechanism of PUFA transfer through placenta

The cellular transportation and physiological actions of PUFAs are mediated by fatty acid binding proteins (FABPs) which are encoded by the intracellular lipid-binding protein gene family[19]. Studies in mammalian cells indicate that placental fatty acid uptake occur through several membrane proteins; fatty acid translocase (FAT/CD36), fatty acid transport protein (FATPs) and plasma membrane fatty acid binding proteins (p-$FABP_{pm}$). It has been previously identified p-$FABP_{pm}$ in placental cells (trophoblast) and proposed the possible involvement of molecules including several membrane associated transporters (FATPs, CD36, and caveolin) and cytoplasmic FABPs (FABP3, and FABP1), all of which are associated with cellular FA trafficking process[20,21]. Among the FABPs, FABP3 is one of the most abundantly expressed molecules in the trophoblast cells[22]. Most recently, our investigation using gene knockout animal model revealed that n-3 and n-6 PUFAs are transported across the trophoblast cell by ferrying function of FABP3 molecule[22]. The detailed mechanism of placental transport of n-3 and n-6 PUFAs have been shown elsewhere[10].

Prenatal PUFA undernutrition and its possible involvement with neuronal development

Adequate PUFAs nutritions for pregnant mothers and infants is necessary for normal brain development, during prenatal development, adequate supplies are so essential that the placenta doubles the levels of nutrients circulating in maternal plasma[23], and severe deficits may have permanent effects if they occur during critical periods of early development. Pregnancy and infancy are important periods for the formation of the brain, laying the foundation for the development of cognitive, motor, and socio-emotional skills throughout childhood and adulthood. Children with restricted development of these skills during early life are at risk for later neuropsychological problems, poor school achievement, early school dropout and low-skilled employment[15, 24].

Many mothers and children in both low-and high-income countries are at risk for moderate undernutrition. Decreased fetal nutrition can be caused by poverty, maternal dieting, teenage pregnancy, and uterine vascular problems. Many children worldwide face these conditions. For example, in 2013, 842.3 million people in the world experienced food insecurity[25] while 14.3% lives in developing countries. Every day in developing countries, 20,000 girls below age 18 give birth[26]. An estimated 200 million children under age five in low- and middle-income countries are at risk of failing to reach their developmental potential in cognitive, motor, and socio-emotional abilities, partly due to undernutrition[27]. An estimated 200 million children under age five in low- and middle-income countries are at risk of failing to reach their developmental potential in cognitive,

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Mechanisms for the effect of PUFA undernutrition on brain development

PUFA undernutrition may influence brain development by directly affecting brain processes. First, inadequate availability of PUFAs during gestation and infancy affects the structural and functional development of the brain. The neural tube begins to form 16 days after conception and within 7 months takes on a form that resembles the adult brain[28]. PUFAs are required for many of the biological processes that drive this transformation. For example, they are needed for the creation of new neurons consisted by a cell body, axon and dendrites. PUFAs are also essential for the growth of axons and dendrites, the formation of synapses, and the covering of axons with myelin. Insufficient supply of FAs, energy, protein, and micronutrients impairs these neurodevelopmental processes[29]. These nutrients are also important for brain function throughout childhood and adulthood, for the maintenance of brain tissue and for neurotransmitter synthesis[30,31]. Recent studies revealed that moderate (30%) reduction in maternal food intake during the first half of pregnancy in baboons negatively affected fetal brain development even though fetal weight was not affected and maternal weight was only slightly affected. This suggests that the brain can be affected by moderate undernutrition during this period even in the absence of overt signs of undernutrition[32]. Our recent studies also revealed that fetal or placental weight conserved although 44% decreased placental PUFAs transportation[22] but adversely affect fetal brain development[33].

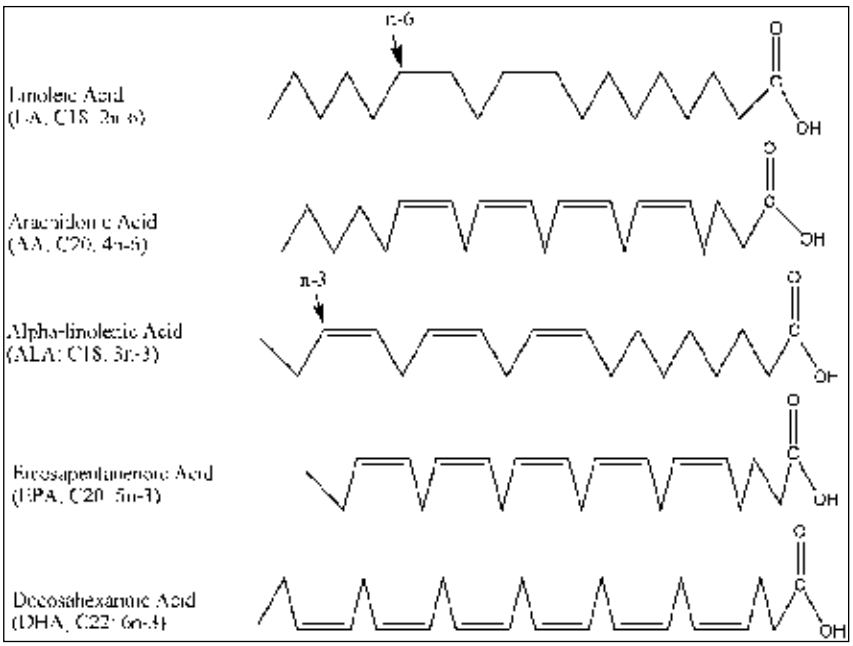

Fig. 1 Structure of n-6 and n-3 PUFAs

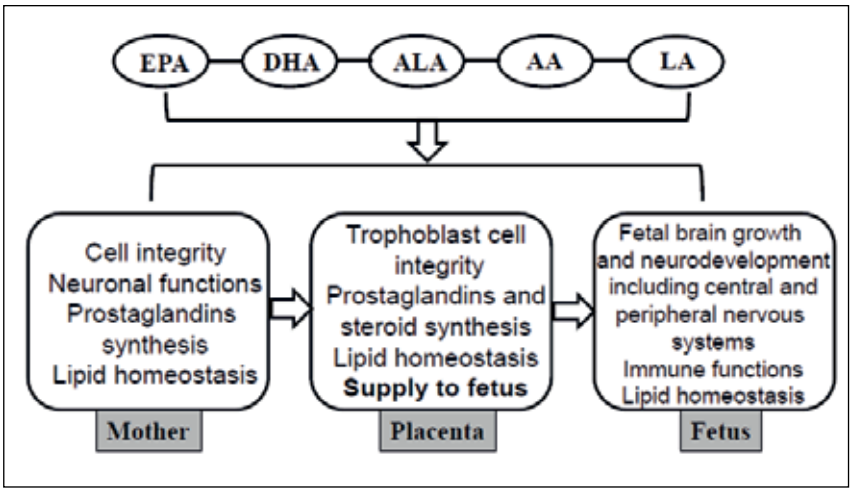

Figure 2. Role of PUFAs in fetal brain development; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid; ALA, α-linolenic acid; AA, Arachidonic acid; LA, Linoleic acid

Poor mental development due to early life undernutrition

Severe acute malnutrition (low weight for height) in early life can have long-lasting consequences on brain development even after nutritional rehabilitation. Many studies have compared school-age children who had suffered from an episode of severe acute malnutrition in utero and in the first few years of life. These studies generally found that those who had suffered from early malnutrition had poorer IQ levels, cognitive function, and school achievement, as well as greater behavioral problems[34]. To treat malnourished children, WHO recommends providing structured activities to promote cognitive development in addition to nutrition and health care. Two studies in Uganda and Bangladesh have shown that providing such stimulation can

improve mental and motor development in severely malnourished infants[35].

Prenatal malnutrition, as measured by poor physical growth, is also associated with reduced cognitive and motor development. From the first year of life through school age, children who are short for their age (stunted) or underweight for their age perform more poorly than their normal-sized peers (on average) in cognitive and motor tasks and in school achievement[36]. Longitudinal studies have also consistently shown that children who had been stunted (height for age < -2 SD below norm values) in the first 2 years of life continued to show deficits in cognition and school achievement from age 5 years to adolescence[36]. Thus, chronic undernutrition in early life seems to have long-lasting consequences for brain development.

DOHaD and adult health risk

DOHaD approach evolved from epidemiological studies of infant and adult diseases, first reported by Barker and his colleagues[37,38] led to the fetal origins hypothesis (often called "Barker's hypothesis"). According to Barker hypothesis child with the lowest birth weights had the highest death rate tendency, while those with the highest birth weights had the lowest death rate tendency, and standardized death rates fell sharply with increasing weight at 1 year of age. To explain more Barker et al[38] showed how fetal undernutrition at different stages of gestation can be linked to different birth phenotypes, each linked to adaptations associated with changes in concentrations of placental and fetal hormone and later with different metabolic abnormalities in adulthood. This integration proposed that "undernutrition during gestation reprograms the relationship between glucose and insulin and between growth hormone and IGF [insulin-like growth factor]"), which permanently changes the body's structure, function and metabolism that increases risk for coronary heart disease in later life.

Epidemic evidence of prenatal malnutrition and its impact on neurodevelopment

Prenatal nutritional deficiency may have severe impact on child brain development as suggested from the studies of the Dutch Hunger Winter (1944–1945) and the Chinese famine (1959–1961). In the former, there was a sharp and time-limited decline in food intake. It lasted from shortly after the Nazi blockade of occupied western Holland in 1944 until liberation in May 1945[39]. There was a 2-fold increase in risk of schizophrenia among children conceived and in early gestation at the height of the famine. In the west Holland, or famine region, birth cohorts exposed to severe food deprivation (an average daily ration under 4200 kJ) during the first trimester showed a substantial increase in hospitalized schizophrenia. Moderate food deprivation during the first trimester (average daily ration under 6300 kJ) was not associated with increased risk of schizophrenia in the famine region. In the north and south regions, numbers were smaller and there was no exposure to severe famine. This study indicates that first-trimester exposure to acute food deprivation is a risk factor for schizophrenia[40].

More than fifty years ago, China encountered world's largest famine: between the spring of 1959 and the end of 1961, some 30 million Chinese starved to death and about the same number of births were lost or postponed. The famine affected all provinces in China. It followed a period of immense social and economic upheaval often called the "Great Leap Forward". The statistical studies from Anhui province revealed that a 2-fold increased risk of schizophrenia among the offspring those were conceived at the height of famine with risk related to severity of famine conditions[41].

Pathophysiological evidence of PUFA undernutrition and neurodevelopmental disorders

Maternal exposure to famine elevated risk for schizophrenia, supporting again an important link between maternal nutrition and offspring neurodevelopment[40,41]. As the brain continues to mature and develop well into adolescence, it is also critical to understand the influence of the postnatal environment on programming of disease risk.

Several studies using either primates or human postmortem sample showed that PUFA composition specially DHA and AA concentration was significantly lower in prefrontal cortex or caudate nucleus; sensitive to normal brain functions[42,43]. Recently it has been revealed that FABPs has been mutated in the postmortem brain resulting altered protein structure that may lead to the development of schizophrenia, autism or other related neuropsychiatric disorders[44,45].

Current evidence for abnormalities of PUFA metabolism in neurodevelopmental disorders

Attention deficit hyperactivity disorder (ADHD)

Deficiency in certain PUFAs as a factor in ADHD is well known since 30 years ago. Recent evidence from blood biochemical and other studies has

revealed that ADHD involves difficulties in the synthesis of PUFAs, rather than a lack of their EFA precursors, although other mechanisms may be involved. Given the heterogeneity of ADHD it seems probable that FA abnormalities would affect a subset of individuals receiving this diagnosis. Findings are broadly in line with the original proposal that n-3 PUFA deficiencies were associated with behavioral and learning problems as well as with some aspects of general health[46].

Dyslexia

More recently, dyslexia has been proposed to be involved with fatty acid abnormalities and followed from reports that certain visual deficits in dyslexic adults could be corrected via treatment with n-3 PUFAs[47]. In one early case report, PUFA deficiency in a dyslexic child was confirmed by biochemical testing, and benefits from PUFA treatment were noted[48]. This child showed the same clinical signs of ADHD, disappeared following PUFA supplementation noted by improvements in schoolwork.

Dyspraxia

Among neurodevelopmental disorders, dyspraxia has probably been the least studied in relation to PUFA metabolism. However, due to high co-morbidity with both ADHD and dyslexia the involvement of PUFA metabolism in dyspraxia cannot be ruled out. It is quite possible that dyspraxic features may help to identify relevant subgroups within dyslexia or ADHD. However Taylor et al.,[49] showed that dyslexia in adults is associated with clinical signs of PUFA deficiency.

Autistic spectrum disorders (ASD)

Plenty of suggestive evidence regarding ASD with abnormalities of PUFA metabolism are available, but little basic/clinical studies. One previous report has suggested an impairment of peroxisomal function to account for an apparent accumulation of very long chain fatty acids in some autistic individuals[50]. In addition to that instability of membrane PUFA has also been observed in schizophrenia. The mechanisms underlying these are still unknown. Clearly, this is an area that deserves further study using biochemical approach to clarify the involvement of PUFAs with neuronal disorders.

Conclusion:

Nourishing a child with adequate amount of essential PUFAs, energy, protein and micronutrients in pre- and post-natal stage is necessary for brain development; it gives a foundation for lifetime sound brain function. During pregnancy, supplementation with multiple nutrients (FAs, protein, glucose, iron, folic acid, thiamine, iodine etc) may be more beneficial than a single micronutrient alone. Some micronutrients are also needed for the conversion of EFAs to DHA and thus may influence development through this mechanism[51]. Severe acute malnutrition or chronic undernutrition are key risk factors for poor cognitive, motor, and socio-emotional development in childhood which may turn to permanent psychiatric disorders in adulthood.

The fundamental relationship between the ideas of a “neural version of DOHaD” and the potential efficacy of PUFAs in psychiatric patients warrants further elucidation. The “neural version of DOHaD” theory would become beneficial if it could be an innovated with neurodevelopmental theory to adequately address the careful investigation of molecular mechanisms of neurodevelopmental disorders by incorporating susceptible genes, environments and their interactions. The results of these investigations may result in a significant impact on the prevention of mental disorders, and the promotion of health in different phases of life, although the concept is still premature at present and needs further consolidation including the experiments using primate.

Conflict of interest: none.

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