Role of Long Chain Polyunsaturated Fatty Acids in Fetal Programming

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Received: February 23, 2018; Published: May 10, 2018

Abstract
Long chain polyunsaturated fatty acid (LCPUFA) particularly docosahexaenoic acid (DHA) as important component is transferred to fetus from mother through placenta for the development of feto-placental unit. LCPUFA also play a key role in the normal fetal development and functional maturation of the brain and central nervous system. Studies have found active and preferential maternal-fetal transfer of DHA across the human placenta and observed an expression of human placental fatty acid binding and transport proteins. DHA is a structural component of membranes and has been shown to play a crucial role in different signalling pathways including angiogenesis, neuronal signalling and inflammatory pathways. Imbalances in fatty acid intake during pregnancy may affect placental growth leading to neuroendocrine function and energy metabolism in the fetus, result in metabolic programming. These polyunsaturated fatty acids, can modify the epigenome through epigenetic mechanism affecting the level and expression of many vital genes.

Keywords: Long Chain Polyunsaturated Fatty Acids; Fetal Programming; Placenta; Docosahexaenoic Acid

Abbreviations
LCPUFA: Long Chain Polyunsaturated Fatty Acid; ω: Omega; COOH: Carboxyl; CH₃: Methyl; ALA: Alpha Linolenic Acid; EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid; AA: Arachidonic Acid; Δ: Delta; GLA: Gamma Linolenic Acid; DGLA: Dihomo-Gamma-Linolenic Acid; ETA: Eicosatetraenoic Acid; PC: Phosphatidylcholines; PA: Phosphatidic Acid; PE: Phosphatidylethanolamine; P: Phosphatidylcholine; PS: Phosphatidylycerine; PI: Phosphoinositides; PG: Prostaglandins; MMPs: Matrix Metallo Proteins; VEGF: Vascular Endothelial Growth Factor; FABPs: Fatty Acid-Binding Proteins; TrkB: Tyrosine Kinase B Receptor; NFκB: Nuclear Factor κB; PPAR γ: Proliferator-Activated Receptor γ; PMEC: Porcine Mammary Epithelial Cells; TLR: Toll-Like Receptor; MDA: Malondialdehyde; GDM: Gestational Diabetes; FATP4: Fatty Acid Transporting Protein 4; CVD: Cardio Vascular Disease; ANGPTL4: Angiopoietin-Like 4; RXX: Retinoid X Receptor; BDNA: Brain Derived Neurotrophic Factor; NGF: Nerve Growth Factor; MTHFR: Methylene Tetrahydrofolate Reductase; CBS: Cystathionine β-Synthase; PEMT: Phosphatidylethanolamine-N-Methyltransferase

Introduction
Fatty acids play a vital role in fetal growth and development during pregnancy [1]. Imbalances in fatty acid intake during pregnancy and lactation may result in permanent alterations in neuroendocrine function and energy metabolism in the fetus [2]. Fetus has limited capacity to synthesize one of the important fatty acid especially long chain polyunsaturated fatty acid (LCPUFA) hence completely depending on LCPUFA transfer across the placenta [3]. There are many compounds of fatty acids such as monoglycerides, diglycerides, triglycerides, and fatty acids. Amongst these, fatty acids are the main components of lipid classes and are important energy substrates comprising of around 30% of the total energy intake in humans [4,5].

Classification of Fatty Acids
Fatty acids are classified as saturated and unsaturated fatty acids based on the double bonds between the individual carbon atoms of the fatty acid chain (Figure 1).
Saturated Fatty Acids

Saturated fatty acids have no double bonds between the individual carbon atoms as these carbon atoms are saturated with the hydrogen atoms (Figure 2). They are found mostly in meat, dairy products and in some vegetable oils like coconut and palm oil [6]. Saturated fatty acids are involved in lipogenesis, fat deposition and apoptosis [7].
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Unsaturated Fatty Acids

An unsaturated fatty acid contains at least one double bond within the fatty acid chain. These unsaturated fatty acids are further classified into mono and polyunsaturated fatty acids. A monounsaturated fatty acid chain contains one double bond and polyunsaturated contains more than one double bond (Figure 3).

![Figure 3: Mono and polyunsaturated fatty acids [68].](image)

Cis and Trans Fatty Acids

Unsaturated fatty acids are classified as Cis and trans based on the configuration of hydrogen atoms bonded to the carbon atoms involved in a double bond. In the cis configuration, the hydrogen atoms are on the same side of the double bond while in the trans configuration they are on opposite sides of the double bond (Figure 4). Many studies have reported that incorporation of trans fatty acids in the membrane phospholipids may alter basic membrane properties which affect their biochemical activities [8].

![Figure 4: Cis and trans unsaturated fatty acids [68].](image)

Omega Fatty Acids

Fatty acids have two ends, the carboxyl (COOH) end and the methyl (CH₃) end. The carbon atom with the first double bond from the methyl end is known as the omega (ω) end. These omega fatty acids are further divided into three groups namely omega 3, omega 6 and omega 9 fatty acids.

Omega 3 and Omega 6 Fatty Acids

Omega 3 fatty acids have a double bond (C = C) at the ω-3 position and are commonly found in marine and plant oils [9]. During pregnancy adequate consumption of omega 3 fatty acids is necessary since they are the building blocks of fetal brain and retina [10] and are also play a vital role in determining the length of gestation [11]. Alpha linolenic acid (ALA; 18:3, ω-3) an omega 3 fatty acid which is called essential fatty acid because it cannot be synthesized by the human body [12]. Another omega 3 fatty acids are eicosapentaenoic acid (EPA; 20:5, ω-3) and docosahexaenoic acid (DHA; 22:6, ω-3) [13] are biologically the most active and functional forms which are synthesised from ALA.

Omega 6 fatty acids are that have a double bond (C = C) at the ω-6 position and arachidonic acid (AA; 20:4, ω-6) is physiologically an important omega 6 fatty acid synthesized by Linoleic acid (LA; 18:2, ω-6). AA is essential for normal growth and development [14] and is the precursor of eicosanoids [15]. The AA and DHA synthesized by their respective precursors by desaturase enzymes [16]. The LA and ALA convert to gamma linolenic acid (GLA; 18:3, ω-6) and stearidonic acid (18:4, ω-3) by delta (∆)-6 desaturase enzyme [17]. The ∆-5 desaturase converts dihomo-gamma-linolenic acid (DGLA; 20:3, ω-6) and eicosatetraenoic acid (ETA; 20:4, ω-3) to AA and EPA, respectively and this desaturase enzyme is also essential for the synthesis of DHA from EPA (Figure 5) [18].
Omega 9 Fatty Acids

In the omega 9 fatty acids, the carbon–carbon double bond is present at the omega 9 position and are commonly present in animal fat and vegetable oil. Oleic acid (18:1, ω-9) is a common monounsaturated fatty acid in human diet [19]. Nervonic acid is another omega 9 fatty acid, which plays an important role in the biosynthesis of nerve cell myelin [20]. Report suggested that plasma nervonic acid is a good candidate biomarker for the depressive state of major depressive disorder [21].

Phospholipids

Phospholipids are the major components of all cell membranes. Most of the phospholipids contain a diglyceride, a phosphate group and a simple organic molecule such as choline, ethanolamine, inositol and serine. Phosphatidylycerolines (PC) are a class of phospholipids that incorporate choline as the head group and can be easily obtained from a variety of readily available sources such as egg yolk or soyabean. These phospholipids have a hydrophilic head and two hydrophobic tails (Figure 6) and consists of a long fatty acid hydrocarbon chain [22]. Phosphatidic acid (phosphatidate) (PA), phosphatidylethanolamine (cephalin) (PE), phosphatidylyceroline (lecithin) (PC), phosphatidylserine (PS), phosphoinositides (PI) are the major phospholipids in the cell membranes.

These phospholipids are also involved in the signal transduction mechanisms in the cell [23]. After absorption from the diet, DHA is incorporated into membranes as components of phospholipids [24]. Recent molecular dynamic modeling of phospholipid bilayers have consistently demonstrated increased membrane flexibility in the presence of DHA [25].

Role of fatty acids

Fatty acids mainly omega-6 and omega-3 fatty acids are known to have an effect on fetal - placental unit during pregnancy. The supply of optimal levels of LCPUFA to the fetus during early life is really essential during pregnancy. This section mainly focuses of role of LCPUFAs in different environment.

LCPUFAs and Diseases

Omega 3 fatty acids play an important role in neuroprotective properties and represent a potential treatment for a variety of neurodegenerative and neurological disorders [26]. Deficiency of omega 3 fatty acids leads to altered brain development result in can have adverse effects on cognition and synaptic plasticity [27].
EPA and DHA have also been shown to suppress endothelial cell activation and reduce allergic diseases [28]. They also reduce the formation of proinflammatory molecules and thereby reduce the risk for cardiovascular diseases [29]. Consumption of vegetables and legumes which are rich sources of ALA is reported to increase the concentration of EPA and DHA in blood and is protective against cardiovascular diseases and inflammation [30]. Increased omega 6 fatty acids in the diet during the perinatal period are reported to lead to the accumulation of body fat which ultimately leads to the early life origins of obesity and metabolic disease [31]. Decreased levels of omega 3 fatty acids and increased levels of omega 6 fatty acids have also been shown to be associated with breast cancer in obese women [32].

**LCPUFAs and Labor**

LCPUFAs are the precursors of prostaglandins which play a key role in initiating and maintaining normal labor [33,34]. Prostaglandins (PG) series 2 namely PGE-2 and PGF-2α are derived from AA and the premature production of these prostaglandins may lead to remodeling of the cervix, ultimately triggering labor by activating matrix metallo proteins (MMPs) [35]. Prostaglandins series 3 are derived from EPA and do not possess any uterotonic activity and inhibit the synthesis of prostaglandins belonging to series 2 [36]. It has been also reported that omega-3 fatty acid supplementation decreases the incidence of preterm birth in high-risk patients by decreasing PGE-2 and PGF-2α in cultured cells [37].

**LCPUFAs and Angiogenesis**

Angiogenesis is a key event in the placenta, the process of vascular remodeling that involves several growth factors, such as vascular endothelial growth factor (VEGF) [38]. DHA has been shown to influence the placenta by stimulating tube formation in the first trimester trophoblast cells and may be mediated via VEGF and also stimulate expression of intracellular fatty acid-binding proteins (FABPs) FABP-4 and FABP-3 which are known to directly modulate angiogenesis [39,40].

**LCPUFAs and Fetal Development**

During early life, the fetus has a limited capacity to convert ALA to DHA and is completely dependent on the maternal source of DHA [41]. Infants acquire DHA from their mothers, either prenatally via the placenta or postnatally through milk [42]. Placental uptake of maternal fatty acids is essential for the growth and development of the fetal-placental unit and the placenta selectively transports AA and DHA from the mother to the fetus. In the human brain, the major accumulation of DHA occurs in late gestation and is paralleled with the maximal neuronal differentiation process (neurogenesis), which consists of drastic morphological and molecular changes. Several studies have shown that deficiency of DHA during the prenatal and postnatal developmental stages lead to a variety of visual, cognitive and behavioural impairments in the offspring [43]. AA is required for the growth and function of the brain and vascular systems, which are the primary biofuels of human fetal growth [44].

**LCPUFAs Role in signalling pathways**

It has been reported that DHA incorporated into the membrane phospholipids differentially affects the activity of membrane-bound receptors and signaling molecules [45]. DHA is a structural component of membranes and has been shown to play a crucial role in neuronal signaling; through BDNF and tyrosine kinase B receptor (TrkB) in the neuronal cell [46]. AA and its metabolites make up a diverse group of signaling molecules which mediate metabolic and endocrine functions of ovarian and placental cell membranes [47]. These LCPUFAs are involved in many signaling pathways for the development of fetus and placenta during pregnancy (Figure 7).

**Figure 7: LCPUFAs and signaling pathways.**
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**Inflammatory pathway**

Inflammation is a normal defence mechanism that protects the host from infection and other insults. EPA and DHA are capable of partly inhibiting many aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from AA and production of pro-inflammatory cytokines [48]. In the inflammatory mechanism EPA and DHA alter the cell membrane phospholipid fatty acid composition, disrupt the lipid rafts further inhibit an activation of the pro-inflammatory transcription factor i.e. nuclear factor κB (NFκB) so reducing expression of inflammatory genes and activation of the anti-inflammatory transcription factor peroxisome proliferator-activated receptor γ (PPAR γ). DHA appears to attenuate inflammatory responses in lipopolysaccharide -challenged in porcine mammary epithelial cells (PMEC) through modulation of Toll-like receptor (TLR)-4 signalling pathway [49].

Recently Razavi., et al. [50] reported significantly decreased levels C-reactive protein and malondialdehyde (MDA) which are the biomarkers of inflammation and oxidative stress after omega-3 fatty acids supplementation together with vitamin D in gestational diabetes (GDM) patients. Recently it has been reported that maternal DHA supplementation in pregnancy decreases placental inflammation, amino acid transporter expression, increased placental protein expression of fatty acid transporting protein 4 (FATP4) and differentially modulates placental nutrient transport capacity [51].

**Oxidative Stress and Antioxidant Defence pathway**

Dietary intervention with omega-3 fatty acids may potentially modulate inflammation and oxidative stress markers related with cardio vascular disease (CVD), metabolic syndrome and cancer [52]. Omega 3 supplementation in pregnant women prevented the oxidative stress biomarkers i.e. hydro peroxides in the mother and neonate during the first months of postnatal life [53]. Animal studies also investigated that n-3 PUFA improves endothelial nitric oxide synthase (eNOS) function and oxidative stress [54,55].

There are speculations that vitamin D and omega-3 fatty acids may improve biomarkers of oxidative stress, and pregnancy outcomes due to their effects on maternal metabolic profiles [56], increased metabolism of bile acids [57] and inhibiting the activation of NF-κB [58].

**Angiogenic signalling pathways**

DHA and other fatty acids including conjugated linoleic acid stimulate angiogenesis in placental first trimester cells by stimulating the expression of major angiogenic factors such as VEGF and angiopoietin-like 4 (ANGPTL4), fatty acids also stimulate expression of intracellular FABP-4 and FABP-3 [59]. It has been reported that the cytosolic FABP4 is involved in angiogenic growth factors- and fatty acid-induced tube formation in first trimester placental trophoblast cells [60].

**Neuroprotective and Neurotrophin signalling**

AA and DHA are required for growth and function of the brain and vascular systems, which are the primary biofocus of human fetal growth. Molecular dynamics and experimental evidence suggest that DHA could be the ligand for the retinoid X receptor (RXR) in neural tissue [61]. Maternal DHA supplementation during pregnancy is linked to better infant neurodevelopment; however, maternal-fetal transfer of DHA is reduced in women with diabetes [62]. The levels of neurotrophins such as brain derived neurotrophic factor (BDNA) and nerve growth factor (NGF) and their receptors i.e. TrKB are regulated by DHA which is an important structural component of the plasma membrane [63]. Fatty acids, particularly omega-6 and omega-3 fatty acids, can have effects on fetal programming by affecting the function of these signalling pathways.

**LCPUFAs and Fetal programming**

Excessive or insufficient fatty acid intake during pregnancy can cause metabolic and endocrine adaptations that affect cell division, cell differentiation, gene expression, and epigenetic modifications. Further all these changes can, cause permanent changes in body composition, adipose tissue, vital organs (like brain and liver), and metabolic and neuroendocrine systems [2]. There are very few studies which indicates changes in the levels of gene expressions through epigenetic mechanisms due to altered levels of DHA [64,65].

**Citation:** Madhavi Dhobale. “Role of Long Chain Polyunsaturated Fatty Acids in Fetal Programming”. EC Gynaecology 7.6 (2018): 199-210.
The altered major phospholipids (DHA) and the levels of glutathione and mRNA levels of the key genes such as methylene tetrahydrofolate reductase (MTHFR) and methionine synthase, cystathionine b-synthase (CBS) and Phosphatidylethanolamine-N-methyltransferase (PEMT) which are encoding enzymes of the one carbon cycle in the rat placenta may also be determined [64]. These changes may also have important implications for the epigenetic programming of the developing fetus. Membrane phospholipids are the major methyl group acceptors and reduced DHA levels may result in diversion of methyl groups towards DNA ultimately resulting in DNA methylation described in one carbon metabolic pathway [65,66]. Recent study indicates maternal DHA supplementation during the second half of pregnancy had small effects on DNA methylation of infants. While the potential functional significance of these changes remains to be determined [67].

There are very limited studies that can explain the altered levels of different signalling molecules due to changes in the levels of fatty acids through DNA methylation in the feto-placental unit. Therefore the altered levels of LCPUFA may also have implications for fetal programming of adult diseases. In future there is a need to study the regulation of different signalling pathways by LCPUFAs via epigenetic mechanisms in utero.

**Conclusion**

Omega 3 fatty acid especially DHA during pregnancy play an important role in increase gestation length, enhance fetal and placental growth further reduces the risk of pregnancy complication such as preeclampsia, preterm pregnancy, low birth weight babies. The altered levels of fatty acids may affect the level and expression of important genes those are involved in placental and fetal development during the period of pregnancy. Future studies need to investigate gene specific methylation of membrane bound receptors and signalling molecules in the placenta in different complicated pregnancies and their association with omega 3 fatty acids.

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**Citation:** Madhavi Dhabale. “Role of Long Chain Polyunsaturated Fatty Acids in Fetal Programming”. *EC Gynaecology* 7.6 (2018): 199-210.
