Maternal Long-chain Polyunsaturated Fatty Acids and Pregnancy Outcome

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Amrita Khaire and Sadhana Joshi

Abbreviations

AA	Arachidonic acid
ALA	Alpha-linolenic acid
DHA	Docosahexaenoic acid
GDM	Gestational diabetes mellitus
IUGR	Intrauterine growth restriction
LA	Linoleic acid
LCPUFA	Long-chain polyunsaturated fatty acids
PUFA	Polyunsaturated fatty acids

Maternal Nutrition and Pregnancy Outcome

The nutritional status of the woman, prior to conception and during pregnancy, is recognized as an important determinant of pregnancy outcome. The pregnant mother provides nourishment for embryonic and fetal growth [1–4] and also prepares her body for labor and parturition [5].

The mother modifies her metabolism early from pregnancy to support the nutritional needs of the fetus [6]. Nutrients transported to the fetus are known to influence cell number and differentiation in the blastocyst that regulates fetal growth and organ development. However, maternal nutritional restriction can lead to fewer cells in the inner cell mass and cause blastocyst abnormalities [7]. Nutrient deficiencies also lead to serious complications of labor, preterm deliveries [8, 9] and contribute to high rates of maternal morbidity and mortality [10, 11]. It also leads to lower birth weight [12], restricted postnatal growth [13], altered organ/body weight ratios [14], and congenital malformations [8] in the offspring.

An adequate and balanced supply of both macro- and micronutrients is critical for maintaining pregnancy and appropriate fetal growth where macronutrients (carbohydrates, proteins, and lipid) provide energy for fetal growth while micronutrients play a major role in the metabolism of macronutrients and are involved in the cellular metabolism of the fetus [10, 15]. Fetal growth and development depends on the unique supply of dietary fatty acids from the mother [16]. Lipids/fats represent a balanced and wholesome diet important to maintain the health and its key components, fatty acids, represent essential nutrients during intrauterine life [6].

Lipids are esters of moderate to long-chain fatty acids, which are carboxylic acids with a long aliphatic hydrocarbon tail, either saturated or unsaturated. Based on the number of double bonds in the hydrocarbon chain, unsaturated fatty acids are further classified as monounsaturated fatty acids (MUFA) (presence of one double bond) and polyunsaturated fatty acids (PUFA) (presence of two or more double bonds).

Long-chain Polyunsaturated Fatty Acids (LCPUFA)

Long-chain polyunsaturated fatty acids (≥20 carbon atoms) are distinguished into two key families; omega-3 and omega-6. Omega-3 fatty acids contain a double bond (C=C) at the third carbon atom from the carboxylic end of the fatty acid chain and omega-6 fatty acids contain a double bond (C=C) at the sixth carbon atom. Among PUFA, linoleic acid (LA; 18:2 omega-6) and alpha-linolenic acid (ALA; 18:3 omega-3) are called 'essential fatty acids' because humans cannot synthesize them in the body and they have to be ingested through the diet [6]. All fatty acids within the omega-3 family are derived from ALA, while all omega-6 fatty acids are derived from LA. Biologically, most active forms of omega-3 PUFA are docosahexaenoic acid (DHA;

A. Khaire · S. Joshi (✉)
Department of Nutritional Medicine, Interactive Research School for Health Affairs, Bharati Vidyapeeth Deemed University, Pune 411043, India
e-mail: srjoshi62@gmail.com

A. Khaire
e-mail: amrita.khaire@gmail.com

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22:6 omega-3) and eicosapentaenoic acid (EPA; 20:5 omega-3). ALA is found in algal oil, flaxseed oil, rapeseed oil (canola), walnuts, and some green leafy vegetables while EPA and DHA are mainly found in marine fish or fish oils. AA is a physiologically important omega-6 fatty acid and is found abundantly in fats, oils, eggs, meat, poultry, cereals, vegetables, nuts, seeds, and human milk.

LCPUFA serve as important constituents of cell membrane phospholipids, play an important role in maintaining the fluidity, permeability, and conformation of cell membranes, perform membrane-associated functions, and act as intracellular mediators of gene expression [17]. AA and DHA are important structural fatty acids in neural tissue. They provide energy, act as the precursors of the metabolically active compounds such as the prostacyclins, prostaglandins, thromboxanes, leukotrienes, and resolvins, and perform functional and structural roles within the body. LCPUFA together with their above-mentioned metabolites are involved in the functioning of transporters, ion channels, and enzymes and in signal transduction pathways [18].

LCPUFA Biosynthesis

Liver is known to play a central role in the fatty acid synthesis and metabolism [19]. Fatty acid desaturases are the enzymes that catalyze the introduction of double bonds at specific positions in a fatty acid chain [20, 21]. Delta 5 (Δ5) and Delta 6(Δ6) desaturases participate in the synthesis of LCPUFA [22, 23]. DHA is endogenously synthesized from its precursor ALA via a series of Δ6 desaturase, Δ5 desaturase, elongase enzymes, and β-oxidation steps [24]. The same series of desaturases and elongases are involved in the conversion of LA into its longer-chain, more unsaturated derivative, AA. These LCPUFA are stored in the adipose tissue in the form of triglycerides.

LCPUFA Metabolism During Pregnancy

There are major changes in the maternal lipid metabolism throughout pregnancy to ensure a continuous supply of fatty acids to the growing fetus [25]. During early pregnancy, LCPUFA consumed through diet are accumulated and stored in the adipose tissue as a result of enhanced lipogenesis. Subsequently in the later stages of gestation, when the fetal growth rate is maximal, there is an increase in the lipolytic activity in the maternal adipose tissue [26, 27]. This increases plasma triacylglycerol concentrations, with smaller rises in phospholipids, cholesterol concentrations [26, 28], and plasma non-esterified fatty acids (a form of free fatty acids present in small proportion) which serve as a source of LCPUFA for the growing fetus. Additionally, there is mobilization of LCPUFA from the maternal adipose tissue depots and selective delivery of maternal circulating LCPUFA to the fetus through placenta [28].

LCPUFA Intake/Status during Pregnancy and Fetal LCPUFA Status

The fatty acid levels in maternal blood lipids serve as indicators of maternal status [29]. Several studies report a decline in the maternal essential fatty acid status from the first trimester of pregnancy until delivery [30]. Additionally, there is depletion in the levels of DHA in maternal total plasma [31], serum [32], plasma phospholipids, and erythrocytes [33, 34]. Report suggests a significant decline in the ratio of DHA to docosapentaenoic acid in maternal plasma phospholipids indicating maternal difficulty during pregnancy to cope up with high demands of DHA [34]. Although these studies provide evidence for compromised LCPUFA status in pregnancy, there is limited information on the maternal factors that influence essential fatty acid metabolism during pregnancy. Presumably, maternal dietary intake/status of LCPUFA is related to the amount of fatty acids delivered to the fetus through the placenta [35, 36]. Since the ability of fetus and placenta to synthesize LCPUFA is low, the fetus primarily depends on placental transfer of LCPUFA [32].

Maternal fatty acid intake can directly influence the plasma and tissue fatty acid profile of the offspring [37]. Infant plasma omega-3 and omega-6 fatty acids and conjugated LA are related to maternal plasma fatty acids [38] while the deficiency of AA and DHA in maternal blood throughout pregnancy results in a suboptimal neonatal DHA status [34]. A study in our department has shown higher levels of DHA and AA in cord blood as compared to maternal blood in terms of pregnancy suggesting that large quantities of maternal LCPUFA are diverted to the fetus [39]. Evidence from several observational studies and randomized control trials (RCT) suggests a positive association between intake of omega-3 fatty acids during pregnancy and birth outcome [40].

Role of LCPUFA in Pregnancy

The different kinds of fatty acids consumed by the mother during gestation are known to influence pregnancy and fetal outcome [6] due to their fundamental roles as structural elements and functional modulators [17]. LCPUFA are required to support the development of the fetus in utero. LCPUFA are required in all stages of pregnancy [1] and play important role in determining length of gestation, initiation of labor, and in placental growth and development [41] (Fig. 35.1).

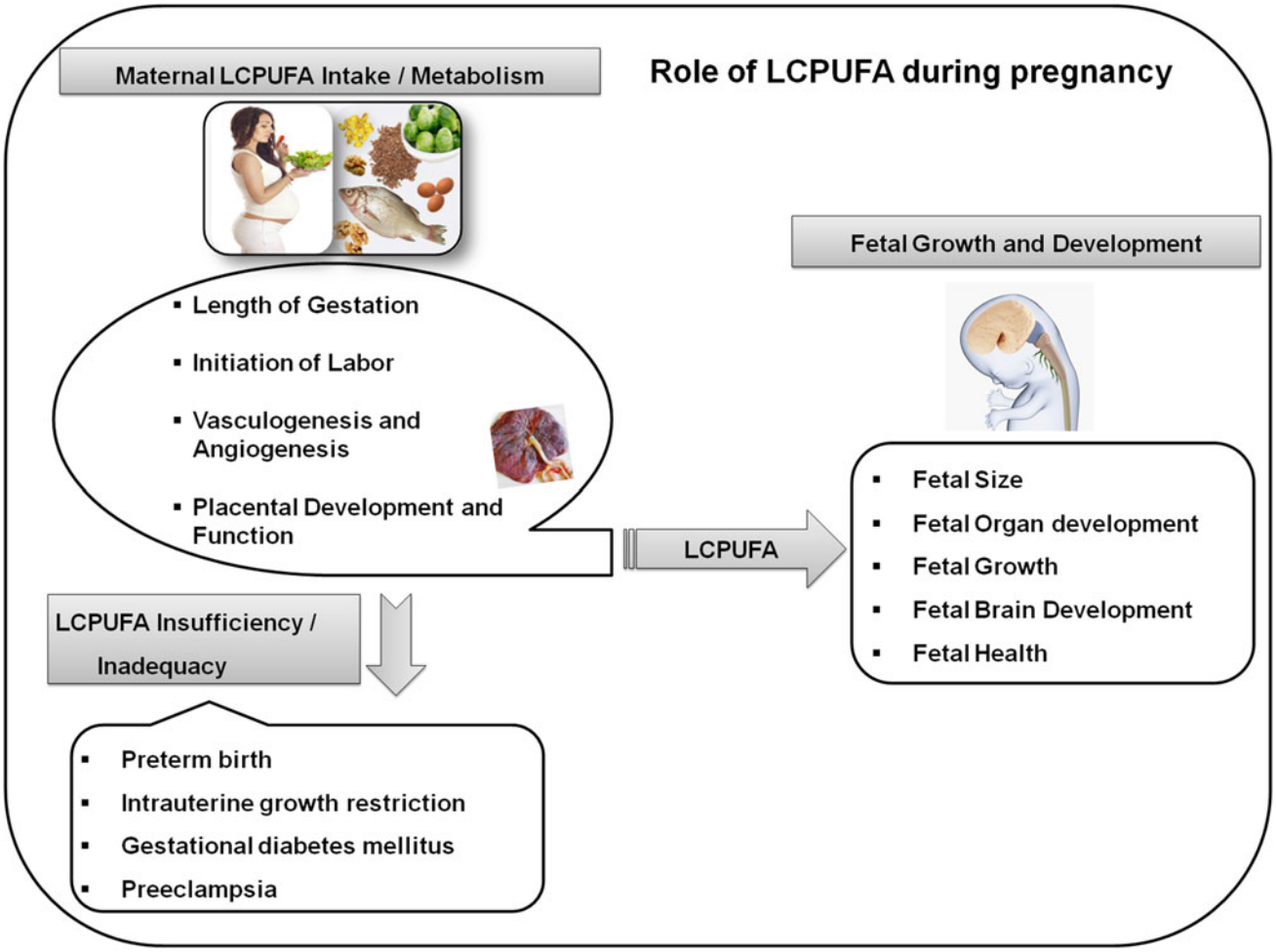

Fig. 35.1 Role of LCPUFA during pregnancy. *LCPUFA* Long-chain polyunsaturated fatty acids. Maternal LCPUFA intake during pregnancy plays an important role in maintaining length of gestation, initiation of labor, placental angiogenesis, and development. However, lower levels of maternal LCPUFA may lead to preterm labor, intrauterine growth retardation, and pregnancy complications such as gestational diabetes mellitus and preeclampsia. Adequate amounts of maternal LCPUFA are essential for fetal growth and organ development, brain development, and overall health

Initiation of Labor

LCPUFA metabolites such as prostaglandins are critical for initiation of labor and parturition process [42]. The rise in prostaglandins is involved in pathway of uterine contractility [43] and their levels increase during labor in the fetal membranes [44].

Among LCPUFA, AA serves as a precursor of the potent 2-series prostaglandins (PGs) E2 and PGF2α, and thromboxane A2 which are required for connective tissue remodeling associated with cervical maturation and rupture of membranes [45, 46]. On the other hand, EPA acts as a precursor for the 3-series of prostaglandins and produces PGE3 and PGI3, which promote myometrium relaxation [42]. These 3-series PGs do not possess any uterotonic activity and inhibit the synthesis of prostaglandins belonging to series 2 [47]. The eicosanoids from omega-3 and omega-6 fatty acids possess opposing modes of action. It is also known that EPA and DHA competitively displace AA in the membrane phospholipids, reduce production of PGE2 and PGF2α, and thereby inhibit the parturition process [48] (Fig. 35.2).

The premature production of PGE-2 and PGF-2α may lead to remodeling of the cervix, ultimately triggering labor by activating matrix metalloproteinases (MMPs) [49]. It has been reported that the concentrations of AA elevate in the amniotic fluid during labor and is accompanied by the elevated levels of PGE2 and PGF2α in the maternal circulation preceding the onset of spontaneous labor [50]. Administration of vaginal PGE2 has been a successful way to induce labor since the 1960s [51, 52].

As the pregnancy progresses, there is a rise in omega-3 fatty acids within the utero-placental unit followed by local production of series-3 prostaglandins, a critical element in cervical

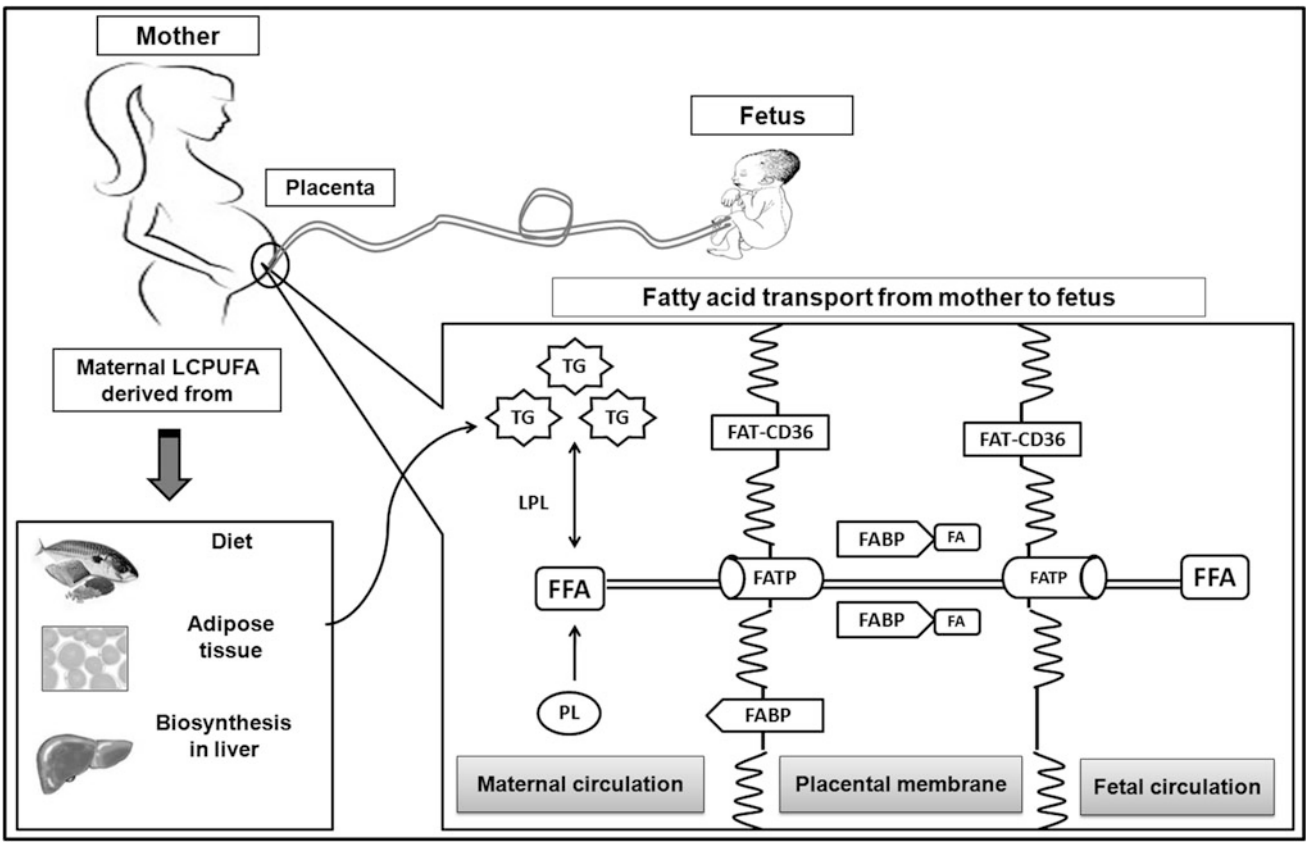

Fig. 35.2 Role of LCPUFA in the maintenance of normal length of gestation and labor. *ALA* Alpha-linolenic acid, *EPA* Eicosapentaenoic acid, *LA* Linoleic acid, and *AA* Arachidonic acid

ripening that plays essential roles in normal initiation of labor [53]. Reports suggest that inclusion of EPA in the diet leads to a reduction in the production of proinflammatory eicosanoids and increased production of prostacyclin (PGI2), promotes myometrial relaxation [54], and prevents preterm labor [55].

Length of Gestation

There is growing evidence that omega-3 fatty acids and their eicosanoid metabolites play vital roles in determining the duration of gestation [54, 56] and parturition process [45]. Improved omega-3 fatty acids status during pregnancy shows promise as series-3 prostaglandins are important in the maintenance of normal length of gestation [57]. Maternal DHA supplementation has shown to increase the length of gestation and infant size [46, 54, 56].

Some RCTs report that 600 mg DHA/d [56] and 800 mg DHA/d [58] significantly increase duration of gestation. On the other hand, 400 mg DHA/d supplementation showed no effect on the gestation duration [59]. No randomized controlled trial has found a reduction in gestation duration or size at birth [56].

LCPUFA in Placental Growth and Development

Placenta is at the interface between mother and fetus and is a key moderator of fetal growth and development [60]. The proper growth, development, and establishment of the placenta with its circulatory system are essential for successful maintenance of mother's health and for the development of the embryo [5].

During pregnancy, vasculogenesis and angiogenesis are critical processes in placental development [61]. Vasculogenesis involves the formation of new blood vessels from angioblast precursor cells, leading to the formation of an initial vascular network. Angiogenesis is the process of development of new vessels from pre-existing blood vessel [62] that plays an important role in the development of capillary network in both maternal and fetal compartments [63]. These processes are regulated by various growth factors, including vascular endothelial growth factor (VEGF) family, placental growth factor (PlGF), transforming growth factor ß (TGF ß) family, and angiopoietins along with proteases such as MMPs as well as their respective receptors [64, 65].

Maternal supply of DHA plays an important role in placental angiogenic processes and vascular remodeling by

increasing the expression of VEGF, angiopoeitin, and tissue inhibitors of metalloproteinases (TIMP) genes [66]. Angiogenic activities of LCPUFA are reported on the first trimester placental trophoblast cell line and have been shown to be highest for DHA followed by EPA and AA [67]. It has been observed that DHA induces maximum tube (capillary-like structures) formation by stimulating cell proliferation in the placenta as compared to other fatty acids [66]. DHA is also known to alter the expression of several genes, such as adipose differentiation-related protein, fatty acid-binding protein-4 (FABP4), FABP3 and cyclooxygenase-2, which are involved in angiogenesis [67]. Studies from our department in women with preeclampsia have shown a negative association between placental DHA levels and maternal anti-angiogenic factor soluble fms-like tyrosine kinase-1 (sFLT-1) levels [68]. A recent review reports that maternal omega-3 fatty acid supplementation during pregnancy is associated with enhanced placental growth and reductions in placental inflammation, oxidative stress in rats [41].

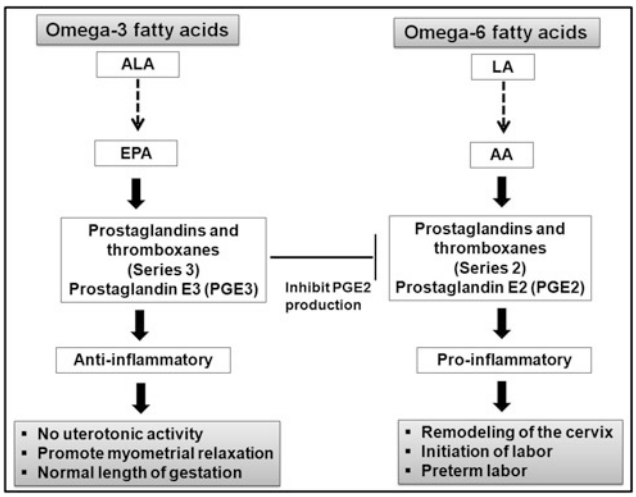

Fig. 35.3 Maternal LCPUFA transport to fetus through placenta. *LCPUFA* Long-chain polyunsaturated fatty acids, *TG* Triglycerides, *LPL* Lipoprotein lipases, *FFA* free fatty acids, *PL* Phospholipids, *FAT* fatty acid translocase, *FATP* fatty acid transport protein, *FABP* fatty acid-binding protein, and *FA* fatty acid

Transport of Maternal LCPUFA to Fetus Through Placenta

The fetus has a limited ability to synthesize LCPUFA because the capacity of the fetal liver for desaturation and chain elongation is not mature in early gestation in humans. Therefore, the fetus is dependent upon the mother for a supply of preformed DHA and AA through placenta. However, maternal lipoproteins which are rich in triglycerides do not directly cross the placental unit and therefore require placental lipoprotein lipases for their hydrolysis to form free fatty acids [26]. These fatty acids are mainly derived from maternal fatty acids bound to albumin, from lipoproteins bound by apoprotein receptors, or from triglyceride-rich lipoproteins released by the triglyceride hydrolases or lipoprotein lipases [69]. These enzymes must be active to facilitate the placental uptake of free fatty acids [70].

The free fatty acids need to get bound with the fatty acid-binding proteins (FABPs; cytosolic and membrane bound FABPs) to get entry into placental cells [46] where they cross the microvillous and basal membranes of placenta by simple diffusion [35]. Additionally, a number of placental fatty acid transport proteins (FATPs) and carrier proteins are present for the transfer of hydrophobic fatty acids from the maternal circulation to the fetal circulation [71] (Fig. 35.3).

Studies from various laboratories have clearly demonstrated the presence of different FATPs both in the cytosol and in the cell membranes and stated their role in the uptake and intracellular transport [72]. Several transport proteins such as plasma membrane fatty acid-binding protein (FATP), fatty acid translocase, or CD36 are located in the placenta to facilitate fatty acid transfer and meet the increased nutrients demand of the fetus during gestation [70, 73]. FATP 1 and FATP 4 have shown to be positively correlated with placental DHA uptake and are important for selective maternal–fetal transfer of DHA [74]. Thus, the placenta plays a critical role in modulating the transport of maternal fatty acids to fetus [41, 75].

Consequences of LCPUFA Inadequacy/Insufficiency

A number of RCTs have demonstrated that the maternal DHA intake during pregnancy can prolong high-risk pregnancies, reduce early preterm delivery, improve birth outcome by increasing birth weight, and head circumference and birth length [1]. However, low concentrations of maternal LCPUFA have shown to be associated with adverse pregnancy outcome, reduced birth weight, and an increased risk of small for gestational age infants [76].

Preterm Labor

Preterm birth is defined as birth before 37 weeks of gestation or fewer than 259 days since the first day of the woman's last menstrual period. As mentioned above, the balance between omega-3 and omega-6 fatty acids plays an important role in the maintenance of normal length of gestation. However, an imbalance between omega-3 and omega-6 fatty acids may lead to disturbances in the production of prostaglandins which are critical in cervical ripening and initiation of labor [57].

Preterm birth is characterized by lower production of prostaglandins by the reproductive tissue [45]. If omega-3 fatty acid accumulation within the feto-placental unit is low and local production of prostaglandins is high, the cervix ripens prematurely with increase in uterine contractions, leading to preterm delivery [57]. Mothers delivering preterm babies are reported to have low levels of omega-3 fatty acids [77]. Additionally, it is reported that the percent total LA, AA, EPA, and omega-6/omega-3 ratio are higher while total omega-3 fatty acids are lower in preterm mothers compared to full-term mothers [77]. An imbalance in the levels of omega-3 and omega-6 fatty acids has been reported in the preterm delivery [47] where a high ratio of omega-6/omega-3 fatty acids results in increased production of PGE2 and PGF2α leading to initiation of labor and preterm labor [54].

Studies from our department have reported reduced erythrocyte DHA levels in mothers of preterm babies as compared to mothers of term babies [78] and reduced levels of placental AA and DHA in preterm deliveries [79]. A study in preterm and full-term human newborns found differences in maternal erythrocyte AA content and hypothesized that high content of maternal erythrocyte AA and AA/EPA ratio may be considered as an early signal of preterm delivery [80]. Similar observations are reported in the fatty acid profile of erythrocyte membrane of Brazilian mothers at delivery [81] and in the fatty acid composition of the colostrum of Iraqi mothers delivering preterm [82].

Supplementation of omega-3 fatty acids during pregnancy has shown to reduce early preterm birth before 34 weeks of gestation by 31 % [83]. Omega-3 fatty acid supplementation has also been reported to reduce the rate of recurrent preterm birth in a randomized trial [84].

Intrauterine Growth Restriction

Normal fetal growth depends on the genetically predetermined growth potential and is modulated by fetal, placental, maternal, and external factors [85]. Intrauterine growth restriction (IUGR) is characterized by the failure of the fetus to reach its genetic growth potential [85, 86] and is associated with increased perinatal mortality and morbidity [86].

LCPUFA status is altered in pregnancies complicated by IUGR [87]. Reports suggest alterations in lipid status in the mother, fetus, and placenta in IUGR pregnancies, i.e., a decrease in the conversion of LA and ALA into AA and DHA, respectively [88, 89]. Abnormal maternal lipoprotein concentrations of cholesterol, low-density lipoprotein (LDL)-cholesterol have been reported in IUGR [90].

A lower proportion of AA and DHA in fetal blood in comparison with maternal blood has been reported in IUGR pregnancies which may be related to inadequate transplacental supply and a fetal lack of desaturases enzymes [88]. Reports suggest that placentas of infants with IUGR have a specific placental phenotype indicating alterations in placental structure and functions [91]. Altered placental lipoprotein lipase activity and placental FABP expression has been reported in IUGR pregnancies indicating disrupted lipid metabolism in these pregnancies [92]. However, only minor changes in passive membrane permeability and composition have been reported in the syncytiotrophoblast membranes in IUGR pregnancies [93]. A case control study reports an increase in AA in the placenta and umbilical artery phospholipids of fetal growth retardation speculating that the differential arterial composition may be responsible for the increased cardiovascular risk of fetal growth-restricted infants in adulthood [33].

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is characterized by an abnormal glucose tolerance diagnosed for the first time during pregnancy [94]. GDM is associated with adverse obstetric and perinatal outcomes [95] and these mothers are at a risk of developing type 2 diabetes in later life [96]. Intake of specific types of dietary fat has been implicated in GDM risk where diets high in saturated fatty acids increase the risk of developing GDM [97] while PUFA are protective [98].

Reduction in plasma phospholipid of omega-6 fatty acids has been reported in GDM mothers [99]. In GDM, decreased proportion of LCPUFA in fetal plasma has been reported resulting from decreased supply, impaired placental transfer, or altered intrauterine metabolism [100]. Altered maternal metabolism, as a result of maternal hyperglycemia in GDM, affects placental metabolism and leads to an aberrant fetal metabolism [101]. In GDM pregnancies, fetal plasma and red blood cells show an altered lipid pattern compared to controls, with reduced AA and DHA levels [102]. On the other hand, elevated levels of DHA and AA in placental phospholipids are reported in GDM, which subsequently results into impaired LCPUFA transport to the fetus [103]. The composition of placental glycerol phospholipids is known to be altered in GDM and might reflect an aberrant fatty acid transfer across the placenta affecting fetal body composition. Placental mRNA and protein expression of CD36 has shown to be higher while FABP1 mRNA and FABP3 protein expression has shown to be lower in GDM [104].

Disturbance in normal fetal growth and development induced by GDM is associated with long-term adverse effects in the offspring, such as adiposity and type 2 diabetes [105]. GDM is associated with increased fetal weight and the risk for later metabolic and cardiovascular diseases [106]. However, omega-3 fatty acid supplementation in GDM pregnancy is reported to have beneficial effects on maternal high-sensitivity C-reactive protein, malondialdehyde levels, and hyperbilirubinemia of newborn babies [107].

Preeclampsia

Preeclampsia is a pregnancy complication manifested by hypertension, proteinuria, and the varying degrees of ischemic peripheral organ damage, which typically arise in the third trimester of gestation [108]. There are limited studies which have reported lower levels of omega-3 fatty acids from erythrocytes in preeclampsia [109, 110]. It has previously been shown that low erythrocyte levels of omega-3 fatty acids and high levels of omega-6 fatty acids particularly AA are associated with an increased risk of preeclampsia [111] while higher levels of omega-3 fatty acids at mid-gestation are associated with lower maternal blood pressures and pregnancy-associated hypertension [112]. A report suggests that high intakes of energy, sucrose, and PUFA independently increase the risk for preeclampsia [113]. Report suggests that lower concentrations of maternal and fetal LCPUFA in mothers with preeclampsia may be due to the decreased maternal LCPUFA synthesis that further leads to deficiency in the offspring [114]. Some studies report no change in the LCPUFA status [109] while others report higher DHA levels [115]. Further, it is likely that altered membrane lipid fatty acid composition may lead to altered placental development in preeclampsia [116]. Reports suggest a possible role of impaired placental fatty acid oxidation in the pathogenesis of preeclampsia [117]. Recent study from our department also indicates that disturbances in placental fatty acid metabolism exist in preeclampsia [118].

Maternal LCPUFA and Fetal Development

Maternal LCPUFA and its storage in fetal adipose tissue provide an important source of LCPUFA during the critical first months of life for rapid cellular growth and activity [28, 119]. It is known that prior to 25 weeks of gestation, the fetus accumulates only a small amount of lipids and thereafter exponentially accumulates large amount of lipids [28]. It has been reported that the fetus requires approximately 50 mg/kg/day of omega-3 fatty acids and 400 mg/kg/day of omega 6 fatty acids during the early weeks of life [120, 121].

Fetal Size and Weight

If adequate nutrition is available, the fetus can reach its growth potential, resulting in the birth of a healthy newborn of appropriate size. Among LCPUFA, DHA has shown to play important role in determining birth weight [46, 122], fetal growth, and development [1, 58]. Placental phosphatidylethanolamine with AA is known to be associated with fetal growth [123]. Low plasma phospholipid concentrations of EPA, DHA, and dihomo-gamma-linolenic acid (DGLA) and high concentrations of AA during early pregnancy have shown to be associated with reduced birth weight and/or an increased risk of small for gestational length infants [76]. DHA supplementation in large studies has shown slightly higher birth weight by about 50 g at delivery [32]. A meta-analysis of 15 RCTs indicates that maternal omega-3 fatty acid supplementations lightly increase birthweight as compared to placebo but show no differences in birth length and head circumference [40]. A double-blind RCT showed that supplementation with 600 mg/day DHA increases birthweight by 172 g [56]. A recent study reports no association between maternal omega-3 fatty acid compositions in gestational week 24 with fetal weight gain [124]. A study investigating birthweight in a fishing community reports increase in the duration of gestation with increased intake of marine fats but decrease in birthweight [125]. No studies have reported a reduction in infant size at birth by LCPUFA supplementation [56].

Maternal LCPUFA and Brain Development

DHA and AA are found in very high concentrations in cell membranes for fetal neural and retinal development and are known to accrete extensively in these tissues during prenatal period [40, 120, 121]. Brain development is known to accelerate during the second half of pregnancy, lasting until late adolescence [126]. The brain growth spurt that takes place from the third trimester of pregnancy until 18 months after birth also correlates well with DHA accretion in brain phospholipids [127]. During this time, the developing brain is sensitive to acute variations in the supply of DHA. Maternal diet, DHA stores, placental transport, and genetic polymorphisms are reported to influence DHA accretion in the fetal brain.

Several human and animal studies indicate that LCPUFA play a vital role in the development and maintenance of the central nervous system and improved cognitive development and spatial memory [128–131]. However, DHA deficiency has shown to cause retarded visual acuity [132], cognitive impairment, cerebellar dysfunction [133], and various other neurological disorders [134].

High-dosage LCPUFA supplementation at mid-pregnancy has shown to be associated with improved intelligence quotient scores of neurodevelopment [135]. Supplementation studies conducted in pregnancy and/or lactation using DHA suggest that DHA could help in improving cognitive outcome of children in later life [131]. Animal studies indicate that LCPUFA promote early brain development and regulate behavioral aspects, memory, and cognitive functions [136]. These studies have proved that supplementation has many beneficial effects such as increased visual acuity [137], reduced hyperactivity [138], and enhanced cognitive functions,

memory, and attention [136]. Studies based on a rat model of Alzheimer's disease suggest that DHA can be used as a therapeutic agent to improve cognitive decline [139].

Maternal LCPUFA and Fetal Health

Maternal plasma triacylglycerols and non-esterified fatty acids are known to correlate with fetal growth and fat mass [140]. Maternal fasting triglyceride levels are significant predictors of the fatty acid composition of the child's muscle membrane [141]. During gestation and lactation, higher levels of AA, EPA, and DHA are positively associated with child's pre- and postnatal growth [142–144].

A review suggests that maternal intake of omega-3 and omega-6 fatty acids in gestation and lactation can impact the developing infant tissue neuroendocrine and metabolic pathways [145]. Recent studies in humans and animals suggest that inadequate levels of omega-3 fatty acids during the prenatal and postnatal periods influences metabolic diseases [146], lean mass [147], and blood pressure in the offspring [148]. Further, prenatal and early postnatal exposures to low omega-3 fatty acids and high omega-6 fatty acids influence adiposity in children [149]. Children with a lower proportion of LCPUFA in their muscle membrane are at a higher risk for developing insulin resistance [150].

An enhanced maternal–fetal omega-3 PUFA status has shown to be associated with lower childhood adiposity [149]. A review suggests that the provision/supplementation of LCPUFA during critical periods of growth, especially from the 2nd trimester of pregnancy to 5 year, can prevent coronary artery diseases in adult life [151].

Animal studies demonstrate that maternal and post-weaning diet containing omega-3 fatty acids improve the lipid profile in the offspring [152, 153]. The beneficial effects of gestational/prenatal omega-3 fatty acid supplementation in reducing risk for metabolic syndrome markers in the hamster [154] and Wistar rat offspring [155, 156] have also been reported. Maternal supplementation with DHA is reported to decrease blood lipid [157] and improve blood pressure in the adult rat offspring [156].

LCPUFA Recommendations During Pregnancy

Fetal DHA requirement increases exponentially with gestational age due to fetal development. Therefore, a daily intake of DHA during pregnancy is recommended by World Health Organization and the Food and Agriculture Organization of the United Nations [158]. It is advisable that pregnant women should ingest at least 300 mg/day of DHA in order to achieve a better pregnancy outcome [159].

In 2002, the Food and Nutrition Board of the US Institute of Medicine established adequate intake levels (AI) for omega-3 and omega-6 fatty acids[160]. The recommendations suggest that human diets should contain minimum 3 % LA and 0.5 % ALA [161]. The recommended dietary allowances for essential fatty acids are 4.5 % of total energy for pregnant women and 5.7 % of total energy for lactating women. It has been suggested that the intake in Indian pregnant and lactating women should be 300 mg; of which, 200 mg should be in the form of DHA [Indian Council of Medical Research, India [162]. In populations consuming fish, it is recommended that during pregnancy two portions of fish should be consumed per week, with one portion of an oily fish such as mackerel, herring, sardines, or salmon [159].

Conclusion

Dietary intake of LCPUFA before and during pregnancy is critical for maternal health and optimal fetal growth. Accretion of AA and DHA in maternal tissues during pregnancy is the major determinant of length of gestation, parturition, placental growth, and development. Insufficiency/decline in the LCPUFA is associated with adverse pregnancy outcomes such as preterm birth, intrauterine growth retardation, GDM, and preeclampsia. Maternal LCPUFA status positively influences postnatal growth, neuro-cognitive development and helps to improve the health of the offspring.

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