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Research Article

Effect of Long Chain Polyunsaturated Fatty Acid (LC-PUFA) Transfer across Human Placenta on Maternal and Fetal Outcome

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Abstract: Long chain polyunsaturated fatty acids (LC-PUFAs) such as docosahexaenoic acid and arachidonic acid have important role in maternal and fetal development. Several studies have provided link between docosahexaenoic acid (DHA) status of mother with visual and cognitive development of her child. Moreover, supplementation of LC-PUFA during pregnancy increases gestation period as well as birth weight of fetus. Placenta preferentially transfers LC-PUFA as a result of selective uptake by syncytiotrophoblast, intracellular metabolism and selective export to fetal circulation. Cellular uptake and intracellular translocation of fatty acid is associated with various membrane associated fatty acid binding proteins such as plasma membrane fatty acid binding protein (FABPpm), fatty acid translocase (FAT/ CD36) and fatty acid transport proteins (FATPs) along with cytoplasmic fatty acid binding proteins (FABPs). FABP pm is preferentially involved in uptake of LC-PUFAs. FATP-4 protein has key importance in mediating DHA transfer across the human placenta. This review summarizes biosynthesis of LC-PUFAs, placental transfer and its effect on maternal and fetal outcome.
Keywords: Long chain polyunsaturated fatty acids, Placental transfer, Fatty acid binding proteins

INTRODUCTION

Polyunsaturated fatty acids (PUFA) like linoleic acid (LA) and α-lenoleic acid (ALA) are the precursor of Long chain polyunsaturated fatty acids (LC-PUFAs) [1]. The LC-PUFA, Aarachidonic acid (ARA) and docosahexanoic acid (DHA) play an important physiological role during pregnancy both for the pregnant woman and to the outcome of her pregnancy. It is also important for growth and tissue development of the fetus and early development of the nervous system [2].

Biosynthesis of Long chain Polyunsaturated fatty acid (LCPUFA)

Long chain polyunsaturated fatty acids (Arachidonic acid and Docosahexaenoic acid) are derived from LA (18:2 ω-6) and ALA (18:3 ω-3)by enzymatic desaturation and chain elongation (Figure 1). ω-3 are mainly present in fish, shellfish, sea mammals and are scarce in land animals and plants, whereas ω-6 mainly derive from vegetable oils[2,3]. Linoleic acid is metabolized to Arachidonic acid (ARA), whereas α-Linoleic acid metabolized to Elcosapentenoic acid (EPA) & to the Docosahexaenoic acid (DHA) [4, 5].

Insertion of double bond at Δ6 position of α-LA (18:3 ω-3) or LA (18:2 ω-6) by Δ6 desaturase synthesize stearidonic acid or gamma-linolenic acid. It is followed by an elongation step and then a second insertion of a double bond at the Δ5 position of the fatty acid by Δ5 desaturaseto form EPA (20:5 ω-3) or ARA(20:4 ω-6). They are further metabolized to docosahaxaenoic acid (DHA) 22:6 ω-3 ordocosapentaenoic acid (DPA) 22:5 ω-6 [6].

Placental transfer of Fatty acid

Physiologically, the fetus may synthesize some saturated fatty acids and monounsaturated fatty acids *de novo* fromglucose. However, long chainpolyunsaturated fatty acids like DHA and ARA do not synthesize by placenta and fetus both due to insufficient desaturase enzyme activity[8]. Also,the amount of LC-PUFA produced from EFA is insufficient to match the *in utero* accretion rate [9]. Therefore, the primary source of LC-PUFA for thefetus is of maternal origin.

Placental membrane made up of endothelium fetal vessel walls, the villous stroma, the cytotrophoblast and syncytiotrophoblast. Placental trophoblast cells arise from embryo & differentiate to perform specialized functions. Cytotrophoblast disappears within gestational week 20 [7].Any substance crossing between the maternal and fetal circulation has to pass through the villous trophoblast which consists of two membranes;

microvillous facing the maternal blood and basal facing the fetal blood (Figure 2). All fatty acids can cross lipid bilayer such as syncytiotrophoblast by simple diffusion & partition as free fatty acid (FFA) derived from lipoproteins [7,10].

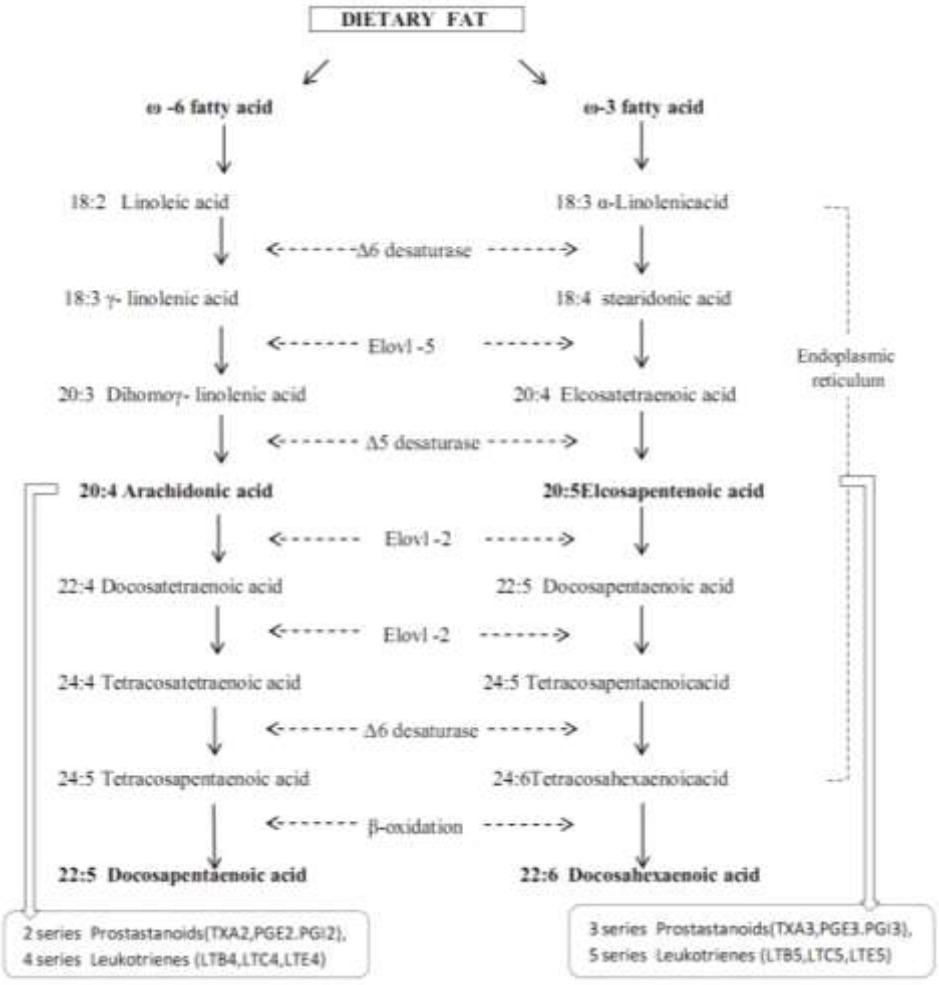

Fig. 1: Biosynthesis of LC-PUFA from essential fatty acids linoleic acid (18:2n-6) and α-Linolenic acid (18:3n-3) [1, 7].

During first two trimester of pregnancy there is an increase in maternal lipogenesis & adipose tissue stores [11].Triglyceride hydrolase or lipoprotein lipase is responsible for hydrolysis of triglyceride rich lipoproteins, i.e. chylomicrons and very low-density lipoproteins (VLDL) Which resulting in free fatty acid transported across the placenta and entering the syncytial placenta cells [12,13].

In placental cell, free fatty acids are esterified with glycerol & resulting triglycerides deposited in Lipid droplets. Lipid droplets are similar to lipoproteins which mediate intracellular lipid storage & lipid metabolism. Lipoprotein lipase is responsible for release of free fatty acid from Lipid droplets [14,15].

In human placenta, Endothelial lipase (EL) and lipoprotein lipase (LPL) are expressed which responsible for hydrolysis of placental lipoproteins. LPL mostly present in placental macrophages While EL was detected in trophoblasts and endothelial cells [16]. As gestation and placental development advance both lipases are significantly down-regulated at the maternal surface of the placenta. At the end of gestation, EL is still expressed, but LPL is virtually absent from the trophoblast [17].

During last trimester of pregnancy and at the time of delivery, free fatty acid concentration difference between maternal and fetal circulation increases by two ways. *First*, lipoprotein lipase activity increase which increases FFA for fetal transport. *Second*, Placenta also partly mobilize fatty acid from adipose tissue through secretion of leptin, a potent stimulator of lipolysis [18, 19].

Various lipid sensing nuclear transcription factors like peroxisome proliferator activated receptor

γ(PPARγ), liver X receptor (LXR), sterol regulatory element binding proteins (SREBP) are critical regulators in cellular homeostasis, which control the expression of several lipid metabolic genes such as fatty acid transporter/binding proteins, lipase, acyl-CoA synthetase. LC-PUFA and their derivatives are potential natural ligands for these nuclear transcription factors [20].

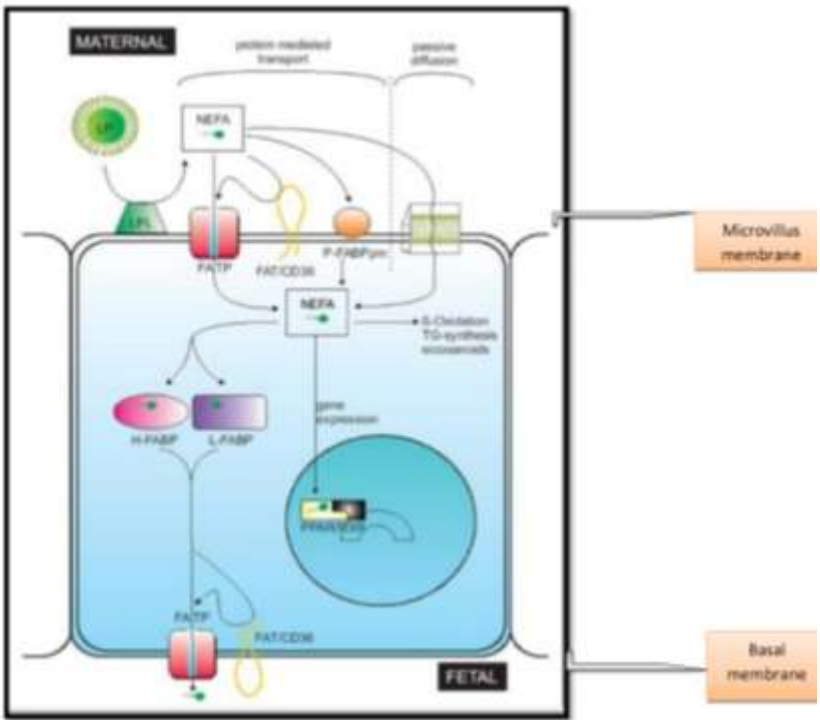

Fig. 2: Figure taken from Hanebutt *et al.* [7]. Fatty acid uptake, Fatty acid metabolism and fatty acid binding/transporter proteins.

Cellular uptake & intracellular translocation of free fatty acid occur through several plasma membrane fatty acid binding proteins& intracellular/cytoplasmic binding proteins. These proteins are located on both syncytiotrophoblast basal & microvillus membrane, except p-FABPpm which is present only in microvillus membrane [22].

Membrane associated fatty acid binding proteins also present in mammalian cell like hepatocytes, adipocytes, cardiomyocytes & jejunal mucosal cell[23].There are several membrane associated binding proteins include 40-kDa plasma membrane associated fatty acid binding protein (FABPpm), the heavily glycosylated 88-kDa fatty acid translocase(FAT) also known as CD36 & family of 63-70-kDa fatty acid transport proteins.(FATP 1-6) (Figure 3) [22, 24, 25].

FAT/CD36 & FATP are the integral proteins while FABPpm is a peripheral membrane protein act as an extracellular fatty acid acceptor [26,27]. FAT & FATP allow transport of FFA bidirectionally from mother to fetus and vice versa, while FABPpm-preferentially binds to LC-PUFA located on maternal side allow transfer to placenta [22, 25, 28].

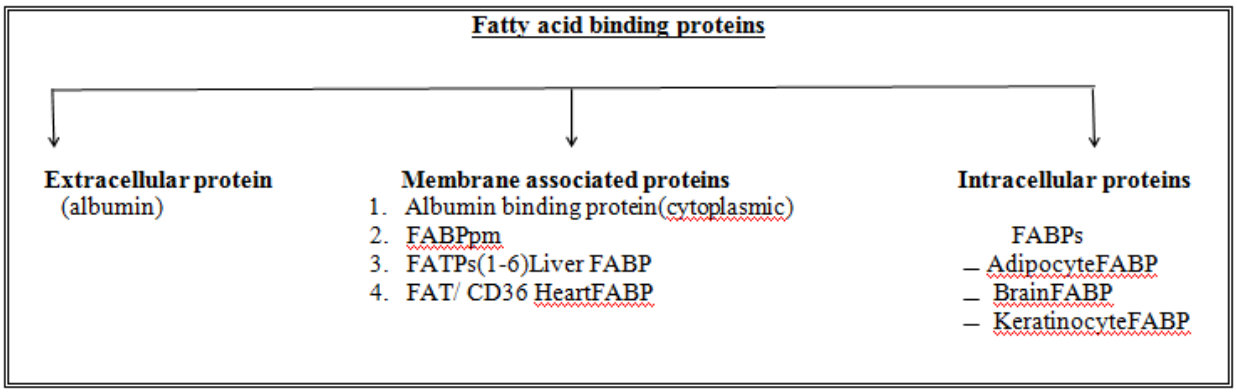

Fig. 3: Proteins associated with fatty acid transport. Plasma membrane fatty acid-binding protein (FABPpm); fatty acid-transport proteins (FATPs); fatty acid translocase (FAT /CD36); Fatty acid-binding proteins (FABPs)

Cytoplasmic/intracellular fatty acid binding proteins (FABPs)

FABPs have different tissue expression patterns. They are described as FABP1 or liver FABP, FABP3 or heart FABP, FABP4 or adipocyte FABP, FABP5 or keratinocyte FABP, and FABP7 or brain FABP. Fatty acid binding protein affinity decrease with decrease chain length & increase with double bond number [29]. Human placental trophoblast demonstrate the presence of cytoplasmic liver type (L-) & heart type (H-) FABP [22]. There are differences in binding activity of these proteins [30]. H-FABP binds only long chain fatty acids whereas L-FABP binds to various growth stimulatory & inhibitory elcosanoids as well as selenium.L-FABP increases fatty acid uptake and also play important role in elcosanoid synthesis in feto-placental unit [23].

Membrane associated fatty acid binding proteins

- **Placental plasma membrane fatty acid binding protein(p-FABPpm)**

  p-FABPpm & FABPpm are peripheral membrane proteins similar in size and membrane location but different in structure (amino acid composition) & function[31]. FABPpmwas first isolated from hepatic plasma membrane and later from major tissues with high transmembrane fatty acid fluxes. This protein is closely related to mitochondrial aspartate aminotransferase (mAspAT) [32]. While, p-FABPpm is located in choriocarcinoma (BeWo) cell of placental microvillus membrane and did not have AspAT activity [31].This protein had higher affinity and binding capacity for LC-PUFA so it is preferentially involved in uptake of LC-PUFA and favours the unidirectional flow of maternal LC-PUFA to fetus [33].

  Study on BeWo cell with anti p-FABPpm revealed that p-FABPpm had higher affinity and binding capacity for LC-PUFA compared with other fatty acids. It inhibits most of uptake of DHA (64%) & AA (68%) whereas OA uptake is inhibited only 32% [31]. The order of antibody mediated fatty acid uptake inhibition was DHA>ARA>>>ALA>LA>>>OA. p-FABPpm preferentially involved in uptake of LC-PUFA by these cells [34].

- **Fatty acid translocase (FAT/CD36)**

  FAT/CD36 (88kDa) is integral membrane proteins having two transmembrane domains with short amino terminal and carboxy terminal and a large multiply N-glycosylated extracellular loop at either ends of the molecule [35]. It is located on the surface of human placenta, platelets, endothelial cells, monocytes, erythrocytes [35-38]. In placenta, FAT/CD36 present in both microvillus as well as basal membrane [22]. It was first investigated during fatty acid uptake by adipocytes[39].It is a multifunctional protein binding with multiple ligands like FFAs, collagen, thrombospondin, and oxidized low-density lipoprotein [35,36,38,40]. It is involved in lipid metabolism, angiogenesis, atherosclerosisand also in inflammation process [28].

- **Fatty acid transporter proteins (FATPs)**

  FATP-1 to 6, gene-solute carrier family 27 (Slc27) could be identified in human & mouse genomes [41].FATPs (63-70 kDa) are integral membrane proteins located on both microvillus as well as basal membranes. FATPs found in skeletal muscle, heart and fat cell in highest level while in brain, kidney, lung & liver in lower level. They have lack of specificity for particular type of FFA so transport occur bidirectionally. FATPs over expression may increase the rate of fatty acid internalization by increasing the rate of "flip flop" trapping the fatty acids [28].

  FATP-1 and 4 located in human placental membranes. FATP-1 affects the lipid metabolism & has potential implication on lipid homeostasis [42]. While FATP-4 has important role in materno-fetal fatty acid transport during early embryogenesis [43]. It acts in concert with enzyme fatty acylCoA synthatase (FACS) that prevent fatty acid efflux and rendering fatty acid uptake unidirectional [28].

Effect of LC-PUFA on maternal & fetal outcomes

During last trimester of pregnancy, women have a significantly higher LC-PUFA requirement due to rapid fetal growth [7]. A Data from meta-analysis on 1278 infants from 6 Randomized controlled intervention trials shows that n-3 LC-PUFA supplementation during pregnancy slightly enhance the length of pregnancy duration (on average 1.57 days) along with increase head circumference (on average 0.23 cm), but the mean effect size is small [44].

A Cochrane review of 6 trials on 2783 women reported that during second half of pregnancy, supplementation of marine oil increases mean gestation that was 2.6 days longer compared with no marine oil treatment. Moreover, Birth weight was also slightly greater in infants born to women in the marine oil group compared with controls [45].

Studies shows that maternal intake of fish and fish oils prolonged gestation by a mean of 1.6 days, increase of birth weight by a mean 47 gms and reduced the risk of preterm birth before 34 weeks of gestation. It was also supported by other independent study, maternal

intake of n-3 LC-PUFA prolonged gestation by a mean of 2.6 days, increases birth weight by a mean 54 gms and also reduced risk of preterm birth by 31% [44,45]. Moreover, High fish consumption lowers the risk of pre-eclampsia. It also has putative role in inflammatory and vascular response altering prostaglandin balance to delay initiation of labour and cervical ripening led to improve major pregnancy outcomes [46]. An enhanced maternal fetal n-3 LC-PUFA is also responsible for lower childhood adiposity [47].

Over-nutrition or imbalance of n-3 LC-PUFA during pregnancy and lactation is associated with sensory/neurological abnormalities and lower body weights in old adulthood. It may occur due to a "nutritional toxicity" during fetal and/or neonatal development that programmed them for life-long health disorder [48].

Docosahexaenoic acid (DHA) is important for long-term cognitive and visual development in neonate. Five-year-old children whose mothers received modest DHA supplementation versus placebo for the first 4 months of breastfeeding period reported better psychomotor development at 30 months of age, suggests that DHA intake during early infancy confers long-term benefits on specific aspects of neurodevelopment [49]. Moreover, Randomly allocated 30 pregnant women supplemented either 200 mg DHA or no DHA and showed improved visual acuity measured in the infants at 4 but not 6 months of age [50].The effect of 400 mg DHA/day or placebo supplementation in 135 pregnant women showed no difference between the DHA and control group in the visual acuity of infants at 2 months of age [50].

Many studies show that depletion in DHA in retinal & neural membrane result in reduced visual function, behavioral abnormalities, altered metabolism of several neurotransmitter and decrease membrane protein, receptor and ion channel activities [51].

CONCLUSION

In fetopla cental unit, preferential transfer of maternal plasma fatty acid is required for fetal growth and development. LC-PUFAs placental transfer occurs through various mechanisms including selective uptake by trophoblast, intracellular metabolism and selective transfer to fetus. Fatty acid transport system consists of multiple membrane binding proteins (pFABPpm, FAT, FATP) and cytoplasmic fatty acid binding proteins (FABPs). p-FABPpm preferentially involved in uptake of LC-PUFA. FATP-4 protein has key importance in mediating DHA transfer across the human placenta. LC-PUFA during pregnancy increase gestation length, increase birth weight and decrease the risk of pre-eclampsia. A further understanding of fetoplacental LC-PUFA transport and its relationship with fatty acid binding proteins are required to improve maternal and fetal outcome.

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