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Review

The ins and outs of maternal-fetal fatty acid metabolism

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Fatty acids (FAs) are one the most essential substances in intrauterine human growth. They are involved in a number of energetic and metabolic processes, including the growth of cell membranes, the retina and the nervous system. Fatty acid deficiency and disruptions in the maternal-placental fetal metabolism of FAs lead to malnutrition of the fetus, hypotrophy and preterm birth. What is more, metabolic diseases and cardiovascular conditions may appear later in life. Meeting a fetus' need for FAs is dependent on maternal diet and on the efficiency of the placenta in transporting FAs to fetal circulation. "Essential fatty acids" are among the most important FAs during the intrauterine growth period. These are α-linolenic acid, which is a precursor of the n-3 series, linoleic acid, which is a precursor of the n-6 series and their derivatives, represented by docosahexaenoic acid and arachidonic acid. The latest studies have shown that medium-chain fatty acids also play a significant role in maternal-fetal metabolism. These FAs have significant effect on the transformation of the precursors into DHA, which may contribute to a relatively stable supply of DHA — even in pregnant women whose diet is low in FAs. The review discusses the problem of fatty acid metabolism at the intersection between a pregnant woman and her child with reference to physiological pregnancy, giving birth to a healthy child, intrauterine growth restriction, preterm birth and giving birth to a small for gestational age child.

Key words: fatty acids, fetal metabolism, pregnancy

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INTRODUCTION

Intrauterine fetal development is a critical period in human development that greatly affects the quality of life in the postnatal period. If the development proceeds properly, the usual outcome is that healthy babies are born at term and are not prone to metabolic or cardiovascular diseases in adult life. The basic precondition of proper intrauterine growth is an appropriate supply of nutrients transported across the placenta. Placental transfer is determined by numerous factors, such as mother's health, condition of the fetus, transport efficiency of the placenta and diet during pregnancy (Haggarty, 2002; Cetin & Alvino, 2009; Cetin *et al.,* 2009). Among the most important nutritional substances are fatty acids (FAs), which are involved in a number of key energy, metabolic and structural processes.

The role of FAs in fetal metabolism can be analysed at two levels: the cellular level and the tissue level. At the cellular level FAs are responsible for the proper development and metabolism of cell membranes as well as for maintaining their appropriate fluidity and permeability. In addition, they are involved in energy processes, in the metabolism of proteins and sugars and regulation of gene expression. They are also precursors of prostacyclins, prostaglandins, thromboxanes and leukotrienes (Haggarty, 2004). At the tissue level they are responsible for the development of the retina, nervous tissue and the brain, which is reflected in children's increased intellectual capabilities when measured later with the use of IQ tests (Gale *et al.,* 2008; Helland *et al.,* 2003). Disturbances in placental transport of FAs usually lead to premature deliveries, which have become an increasingly serious medical and social problem. According to the World Health Organisation (WHO), an estimated 15 million babies are born preterm. They require time-consuming, specialist care in the first weeks of life and, in the long term, they need also treatment for many medical conditions, including chronic diseases, such as diabetes, cardiovascular conditions, etc.

THE INFLUENCE OF A PREGNANT WOMAN'S DIETARY FAT ON FETAL DEVELOPMENT

During pregnancy, a mother's body deposits fat in an amount which corresponds approximately to the baby's weight (3500g) (Hytten, 1974). Fat deposition is most intense during the first and second trimesters of pregnancy (the anabolic period). The main purpose of maternal fat deposition is to transfer some of the deposits to the developing fetus. The body weight of a pregnant woman and the fat mass in her adipose tissue increase — even if the mother is malnourished (Prentice & Goldberg, 2000; Herrera, 2002; Herrera *et al.,* 2006). During fat deposition the levels of phospholipids, non-esterified fatty acids and triglycerides (TG) increase in the maternal circulation. This mechanism is associated with an insulin-dependent decrease in lipoprotein lipase activity in adipose tissue and subsequent insulin resistance. The nutritional requirements of the fetus increase considerably during the third trimester of pregnancy, reflecting the fetus' substantial growth. This is the catabolic period for fat metabolism, including the mother's FAs, due to

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Abbreviations: AA, arachidonic acid; AGA, appropriate for gestational age; ALA, α-linolenic acid; C10:0, capric acid; C12:0, lauric acid; C14:0, myristic acid; DGLA, dihomo-gamma-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; FABP, fatty acid binding protein; FABPpm, plasma membrane fatty-acid binding protein; FAT, fatty acid translocase; FATP, fatty acid transport protein; IUGR, intrauterine growth restriction; LA, linoleic acid; LCPUFA, long chain poly-unsaturated fatty acid; MCFA, medium-chain fatty acid; PL, phospholipid; SGA, small for gestational age; SCFA, short-chain fatty acid; VLDL, very low density lipoproteins

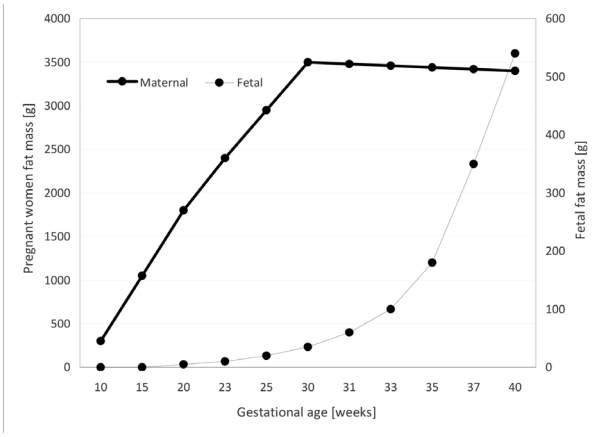

Figure 1. Changes in fat content in pregnant women and the foetus during physiological pregnancy (Hytten, 1974; Widdowson, 1968).

maternal lipolysis. Increased lipolysis results from the decreased sensitivity of insulin receptors, which are hormonally controlled by progesterone, cortisol, prolactin and leptin (Cousins, 1991; Catov *et al.,* 2007). Oestrogens also promote high levels of lipids in the blood circulation of pregnant women. They inhibit the activity of hepatic lipoprotein lipase and increase intestinal absorption of dietary fats (Cetin & Alvino, 2009). These physiological changes in the maternal metabolism increase the concentration of circulating free fatty acids (FFAs) and glycerol, which are substrates for hepatic biosynthesis rich in TG very low density lipoproteins (VLDL). During the catabolic phase the TG concentration in the fasted state is twice as high as the peak postprandial TG concentration recorded in women who are not pregnant (Cetin & Alvino, 2009). The dynamics of changes in the fat content of fetal tissue is different from that found in the mother. Firstly, there is no catabolic period. Secondly, the anabolic period starts much later than it starts for the mother, that is, around weeks 20-22 of pregnancy. The increase in fetal fat occurs gradually over the following 10-12 weeks (Fig. 1) and no sharp increase in fat is observed until approximately week 32 of pregnancy. This period of net mobilisation corresponds to an exponential increase in fetal fat during which 94% of all fat deposition in the fetus occurs (Widdowson, 1968). To make the fat accretion process effective and to guarantee proper fetal development, the mother should eat an appropriate amount of fat of a suitable composition.

DIETARY FATTY ACIDS

According to "Dietary guidelines for Americans" (2005 U.S. Department of Health) fats should constitute about 20–35% of calories consumed (Cetin & Alvino, 2009; FAO 2010). In line with current recommendations and expert opinions, fatty acids should be a key component of the diet of pregnant women. From the physiological point of view, the most important role in maternal-fetal metabolism is performed by long chain poly-unsaturated fatty acids (LC-PUFA) (Cetin *et al.,* 2005; Koletzko *et al.,* 2008; Innis, 2007b; Innis, 2007c; Smithers *et al.,* 2008); the most important of which include the so called "essential fatty acids" α-Linolenic (C18:3 n-3; ALA) and Linoleic acid (C18:2 n-6; LA) (Fig. 2). These FAs are not synthesized by the body and thus, their only source is the mother's diet. ALA and LA are precursors for other, biologically important, long chain-polyunsaturated fatty acids (LC-PUFA). Derivatives of ALA are represented by docosahexaenoic acid (C22:6 n-3; DHA), necessary for brain development (Innis, 2005) and eicosapentaenoic acid (C20:5 n-3; EPA), a precursor of numerous prostanoids and leukotrienes. LA is converted to dihomo-gamma-linolenic acid (C18:3 n-6; DGLA) and arachidonic acid (C20:4 n-6; AA), which are later converted to subsequent derivatives fundamental for immune response, such as prostaglandins, thromboxanes and leukotrienes (Haggarty, 2002; Cetin & Alvino, 2009; Haggarty, 2004).

The recommended daily intake of DHA, EPA and AA

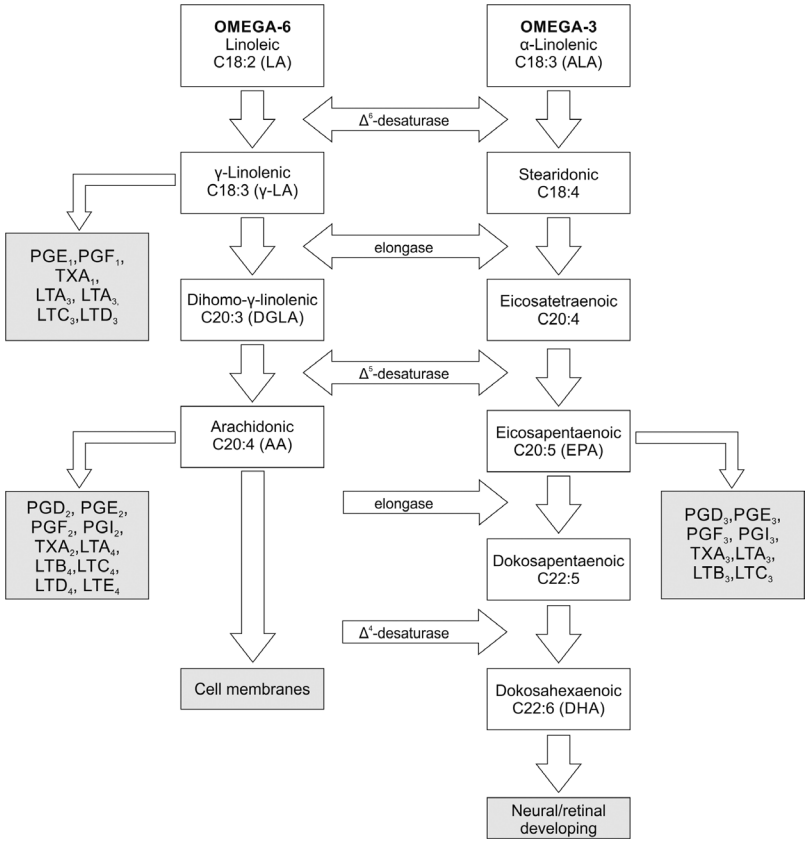

Figure 2. Scheme of metabolism of linoleic (n-6) acids and alpha-linolenic (n-3).
The figure presents only the most important changes connected with the extension of carbon chains that lead to the creation of LCPUFAs and their metabolites, prostanoids and leukotrienes, which are essential in foetal development. Owing to the lack of some elongases and desaturases in the placenta, the biosynthesis of the most important LCPUFAs, such as AA, DHA or EPA, takes place in the mother and partly in the liver of the foetus.

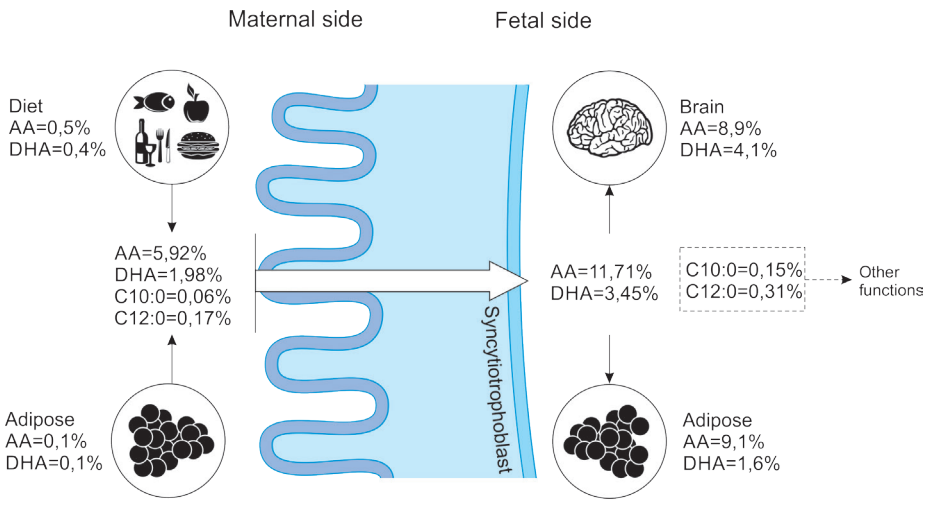

Figure 3. Percentage level of selected fatty acids in maternal diet, adipose tissue of mother and foetus, brain of foetus, maternal blood and cord blood.
The content of all of the fatty acids presented in the figure constitutes proportions of total fatty acids in maternal diet (Otto *et al.*,1997), maternal adipose tissue (FAO, 2008), foetal brain and adipose tissue (Clandinin *et al.*, 1981), and maternal and cord blood plasma (Bobiński *et al.*, 2013b).

for pregnant women is as follows: DHA=200 mg/d, DHA+EPA=300 mg/d and AA=800 mg/d (FAO, 2008). These amounts should meet the needs of the fetus and promote proper nervous system development as well as decrease the risk of preterm birth and/or low birth weight. The dynamics of changes in fetal n-3 and n-6 composition are similar to the dynamics of changes in total fat deposition in the fetus. The fat content, including that of n-3 and n-6, increases in the maternal organism during the final ten weeks of pregnancy (Haggarty, 2004). A specific gradient of LC-PUFA is created between the mother and the fetus, that is a result of the increase in placental transport activity. The process is reflected in the difference in DHA and AA concentrations in the blood of the mother vs the fetus. During the final weeks of pregnancy, the DHA and AA content in fetal plasma is almost twice as high as in the mother's blood. The FAs are absorbed from fetal circulation and stored in fetal adipose tissue. As a result, towards the end of the pregnancy, their levels are several times higher in fetal adipose tissue than in the maternal adipose tissue — sixteen times higher in the case of DHA and over ninety times higher in the case of AA (Fig. 3) (Haggarty, 2002; Leaf *et al.,* 1995; Otto *et al.,* 1997; Lakin *et al.,* 1998; Clandinin *et al.,* 1981; Jansson *et al.,* 2006). The core issue surrounding n-3 and n-6 intake in a mother's diet is not only the amount of the fatty acids (FA) but also the relative proportions of these FAs. Currently, pregnant women are advised to consume oily fish, rich in n-3 FAs because of its beneficial effects on vascular function. In addition, it is generally assumed that the consumption of oily fish may also be beneficial for the development of the fetus's brain and retina. It is worth mentioning, however, that very high intakes from marine sources — particularly in the form of supplements — may not be beneficial for the developing fetus and may not be entirely free of risk (Haggarty, 2004). This problem stems from the common metabolic pathway of n-3 FAs and n-6 FAs in the processes of desaturation and carbon chain extension. The reactions are catalysed by two desaturases: Δ-5 and Δ-6. If the diet of a pregnant woman is abundant in fish and seafood, the increased amount of EPA may — through inhibition of Δ-5 desaturase — slow the creation of AA and its derivatives (Koletzko *et al.,* 2008; Lafond *et al.,* 2000; Llanos *et al.,* 2005). If the maternal diet is rich in plant oils, such as sunflower-seed oil, safflower oil or corn oil, which contain large amounts of LA, then less DHA is produced from ALA as a result of Δ-6 desaturase inhibition leading to decreased EPA biosynthesis. The imbalance between dietary n-3 and n-6 FAs may lead to structural changes in cell membranes in which the composition of LCPUFA lipid fraction is dependent on current LCPUFA concentration in maternal blood. The cell membrane AA content decreases in women consuming foods rich in EPA and DHA. This consequence may have an impact on the duration of pregnancy and on intrauterine fetal development. Studies have shown that n-3 and n-6 deficiencies and changes in the relative proportions of n-3 and n-6 also correlate with placental mass and a low value for fetal/placental mass quotient (Cetin *et al.,* 2002; Cetin *et al.,* 2001). An evaluation of the mutual influence of EPA and DHA contained in the maternal diet and in the maternal-fetal metabolism was performed using laboratory animals. To this end, the diets of two groups of pregnant female rats were enriched with fish oil and olive oil respectively. Lower AA, lower vitamin E and delays in development were found in the offspring of the former group (Smithers *et al.,* 2008; Pardi *et al.,* 2002). Similar changes were not observed in the offspring of the later group. The diet of the first group of females was then enriched with Dihomo-gamma-linolenic acid (DGLA) which is a precursor of AA. As a result of this modification both the AA levels in the offspring in the subsequent litter and their overall development were normalised. This research demonstrates that the mere presence of LCPUFA in the maternal diet is insufficient to guarantee proper development of the fetus, and that this is, in fact, highly dependent on the composition and relative proportions of n-3 and n-6. Optimum intake of the latter reduces the risk of preterm birth and intrauterine fetal underdevelopment, as well as lower the chances of major changes in the child's nervous system, which can have long term negative consequences.

LCPUFAs *VERSUS* MCFAs

The influence of FAs of the n-3 and n-6 series on fetal development is currently the subject of intensive research. The role of ALA, LA, DHA, AA and others of the n-3 and n-6 series in the maternal diet and in maternal-fetal metabolism has been reasonably well recognised. Insufficient consumption of these fatty acids (below recommended standards) during pregnancy may

disrupt the progression of the pregnancy and is often correlated with preterm birth or intrauterine growth restriction (IUGR) (Cetin *et al.,* 2002; Cetin *et al.,* 2001). Recent studies have shown that medium-chain fatty acids (MCFAs) also play an important role in maternal-fetal metabolism (Bobiński *et al.,* 2015a; Bobiński *et al.,* 2015b; Bobiński, *et al.,* 2015c; Nasser *et al.,* 2010; Bobiński *et al.,* 2013a, Bobiński *et al.,* 2013b). Changes in MCFA content have been observed in cord blood, breast milk and diet of pregnant women who gave birth at the junction of physiology and pathology (Bobiński, 2015a). Studies of the diets of mothers who gave birth to "late" preterm neonates (weeks 35–37) or who gave birth to full-term infants who were small for gestational age (SGA), where APGAR scores (Appearance, Pulse, Grimace, Activity, Respiration) in both groups were 9–10, have found a smaller intake of medium-chain fatty acids (MCFAs) and short-chain fatty acids (SCFAs) (Bobiński, 2015a) compared to women who gave birth to healthy neonates on time (AGA) (Table 1). Whereas, the breast milk of women who gave birth to preterm or SGA neonates contained more MCFAs compared to women who had healthy full term neonates (Bobiński *et al.,* 2015a; Garg *et al.,* 2005). Hence, there is a negative correlation between the amount of MCFAs consumed and their content in breast milk. These research results raise the question of the physiological role of MCFAs in prenatal and postnatal child development. Are there any relationships between maternal-fetal metabolism of the n-3 and n-6 series of FAs and MCFAs? The physiological role of MCFAs is connected mainly with energetic and metabolic processes. MCFAs constitute an optimal substrate in the mitochondrial process of energy production that is particularly important for neonates — especially for immature neonates whose enzymatic systems are inefficient and whose demand for energy is very high. MCFAs are preferentially hydrolysed in the intestines: transporting them to mitochondria does not require a carnitine conveyor, so that ATP molecules, precious for a neonate, are not consumed (Bobiński *et al.,* 2013a). The metabolic role of MCFAs is broader and includes a number of processes. Using animal models, investigators have established that lauric acid (C12:0) may affect n-3 metabolism (Legrand, 2010). Under certain conditions this FA may be a precursor of LCPUFA of the n-3 series (Fig. 4) It has been observed that the liver of rats is capable of slow conversion of C12:0 to the mono-unsaturated C12:1 n-3. This may lead to conversion of C12:1 to ALA by Δ6-desaturation, elongation, Δ5-desaturation and two final elongations (Legrand *et al.,* 2002; Jan *et al.,* 2004), especially in extreme physiological circumstances such as a prolonged lack of n-3 in the diet. If such processes take place in humans, there is a possibility that DHA will form from lauric acid, which substantially changes many fundamental issues in maternal-fetal metabolism and the nourishment of pregnant women. What is more, it also extends our knowledge of the physiological role of MCFAs. Studies have shown that myristic acid (C14:0) also affects n-3 and n-6 metabolism and may activate the conversion of ALA to DHA (Legrand *et al.,* 2002). In cultured rat hepatocytes, myristic acid had a specific and dose-dependent effect on Δ6-desaturase activity (Rioux *et al.,* 2005). Based on *in vivo* tests, Rioux showed that when myristic acid was supplied for two months in the diet of rats (0.2–1.2% of dietary energy), with a similar level of dietary ALA (1.6% of FA, 0.3% of energy), a dose response accumulation of EPA was observed in the liver and plasma (Dabadie *et al.,* 2005). Similar results were obtained in research on human diets. Comparing a diet containing 0.6% of myristic acid with a diet containing 1.2% of myristic acid over a 5-week consumption period significantly enhanced EPA and DHA levels in the plasma phospholipid fraction (PL) and DHA level in the plasma cholesteryl esters (Dabadie *et al.,* 2006; Sola *et al.,* 2007). An increase in myristic acid consumption from 1.2% to 1.8% resulted in a decrease in plasma level PL and EPA. This result suggests that the effect of myristic acid on circulating n-3 LCPUFA follows a U-shaped curve with a favourable turning point at around 1.2% of total daily energy (Rioux *et al.,* 2005). In addition to participating in fat metabolism, myristic acid is involved in regulating protein activation by N-myristoylation. The myristoyl moiety has been shown to mediate protein subcellular localisation, protein-protein interaction or protein-membrane interaction (Rioux *et al.,* 2005; Jan *et al.,* 2004). Myristoylation of histone proteins in a chromatin area may regulate the transcription processes of genes located in that area. This process may therefore affect the expression of genes in the fetus, as well as its development. These processes, however, are currently poorly recognised.

The data presented suggest a relationship between n-3 and n-6 metabolism and MCFAs, while also demonstrating the significant role of MCFAs in fetal development (Fig. 4). MCFAs also have a beneficial effect on the metabolism of maternal fat because they undergo fast liver oxidation and are not stored in adipose tissue. According to one of the hypotheses, medium-chain TGs have an inhibitory effect on apoB synthesis and reduce VLDL secretion by hepatocytes (Geliebter *et al.,* 1983, Tachibana *et al.,* 2005). While the currently valid nutrition standards for pregnant women include recommendations on the daily consumption of selected n-3 and n-6 FAs, there are no such guidelines for the intake of MCFAs. It

Table 1. Fatty acid composition of maternal diet in the last month of pregnancy.
The values in the table are expressed as g/day (Bobinski *et al.,* 2015a). AA, arachidonic acid; AGA, appropriate for gestational age; ALA, α-linolenic acid; C10:0, capric acid; C12:0, lauric acid; C14:0, myristic acid; DHA, docosahexaenoic acid; PTB, preterm birth; SGA, small for gestational age.

Fatty acid	Mothers AGA	Mothers PTB	Mothers SGA	*p* Value for Significant Results <0.05
ALA	2.95	2.38	2.71	No
LA	13.96	11.26	11.31	No
DHA	0.16	0.13	0.13	No
AA	0.13	0.12	0.12	No
C10:0	1.09	0.86	1.04	Yes AGA:PTB
C12:0	1.45	1.16	1.35	Yes AGA: PTB
C14:0	4.86	3.94	4.58	Yes AGA:PTB

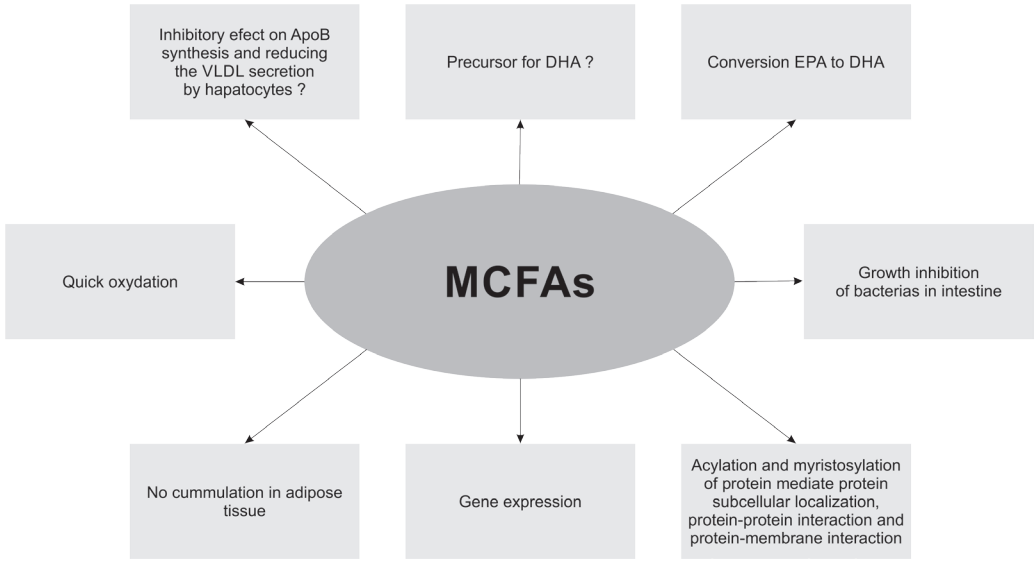

Figure 4. The influence of medium-chain fatty acids (MCFAs) on systemic metabolism

would seem that these recommendations should be reviewed and that at least three MCFAs – capric acid, lauric acid and myristic acid – should potentially be added to the recommended daily intake.

THE ROLE OF THE PLACENTA IN FATTY ACID METABOLISM

The deposition of fatty acids in the fetus does not depend solely on the levels of said FAs in the mother's diet. The placenta has a significant impact on the transport of FAs from the maternal to the fetal circulation (Larqué *et al.,* 2014, Brett *et al.,* 2014). Fatty acids have to pass through the villous trophoblast, which consists of two membranes: the microvillous facing the maternal bloodstream and the basal facing the fetal bloodstream (Haggarty, 2002; Duttaroy *et al.,* 2009a). The difference in FA concentrations in the maternal blood and in the cord blood creates a gradient enabling the transfer of FAs to the fetus by simple diffusion. Specialized fatty acid binding proteins (FABPs), which are located in the microvillous and basal membranes of syncytiotrophoblast cells (Fig. 5) (Haggarty, 2002) also contribute to the placental transfer of FAs. Three types of FABPs can be found in the microvillous membrane which directly faces the maternal bloodstream. The first type is the plasma membrane fatty-acid binding protein (FABPpm), which has a molecular mass of approximately 40 kDa and can be found throughout the body. One of the ways in which the placental FABPpm isoform differs from the other types is its selectivity for fatty acid binding activity in maternal blood (Kaufman & Scheffen, 1998; Campbell *et al.,* 1998). FABPpm binds only 10% of total fatty acids — mainly AA (98%), DHA (87%) and smaller quantities of LA and OA (oleic acid) (Schmitz & Ecker, 2008). FABPpm fulfils the role of an extracellular acceptor of non-esterified fatty acids whose operational mechanism is based on binding the FAs from the maternal cardiovascular system and enabling their diffusion through the lipid membrane by creating a local gradient of FAs between the intracellular and extracellular spaces.

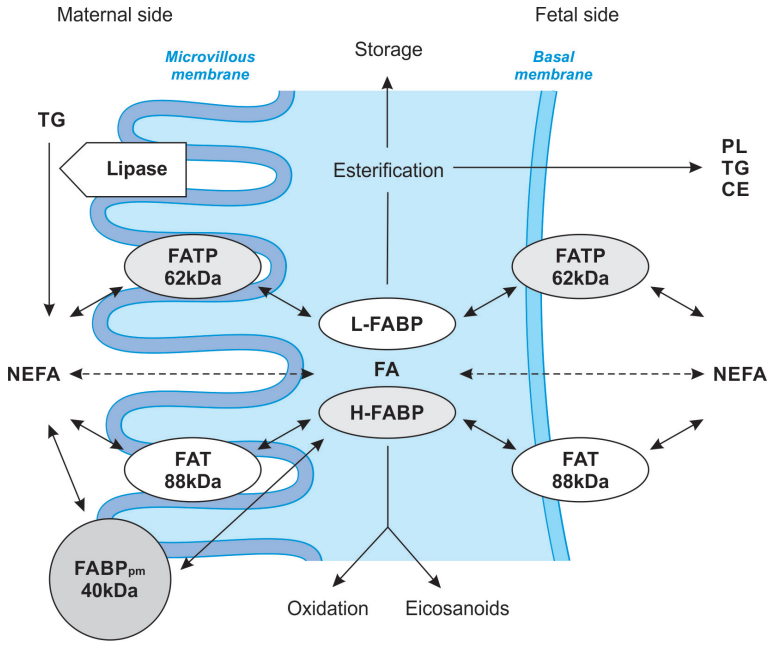

Figure 5. Fatty acid metabolism in syncytiotrophoblast cells.
FABPpm, plasma membrane fatty acid-binding protein; FATP, fatty acid transport protein; FAT, fatty acid translocase; L-FABP, liver-type fatty acid-binding protein; H-FABP, heart-type fatty acid-binding protein; TG, triglyceride; FA, fatty acid; NEFA, non-esterified fatty acid; PL, phospholipid; CE, cholesterol ester.

Fatty acid translocase (FAT/CD36) is the second type of protein involved in placental transfer of FAs. The sequence of FAT/CD36 is 85% homologous with that of glycoprotein IV (CD36). FAT is a highly glycosylated polypeptide chain with an apparent molecular mass of 88 kDa, which is present in both of the placental membranes: microvillous and basal. Unlike FABPpm and FATP, FAT is a multifunctional protein that interacts with a number of ligands

such as free fatty acids (FFAs), collagen, thrombospondin, oxidized LDL and others (Thorburn, 1991; Challis *et al.,* 1998; Challis *et al.,* 2002; Helliwel *et al.,* 2004; Lundin-Schiller & Mitchel, 1990; Alvino *et al.,* 2008). FAT participates not only in FA metabolism but also in angiogenesis, atherosclerosis and inflammation (Kaufman & Scheffen, 1998). FAT is a transmembrane protein functioning as a system which transports or translocates fatty acids to the cytoplasm of syncytiotrophoblast cells in a process that has yet to be explained (Cetin *et al.,* 2009; Cetin *et al.,* 2005; Schmitz & Ecker, 2008; Cetin & Alvino, 2009; Cross, 2006; Duttaroy, 2000; Duttaroy, 2009).

The third protein involved in the placental FA metabolism is fatty acid transporter protein (FATP), which can be found in microvillous and basal membranes. So far, six isoforms of FATP have been identified, each having different tissue expression patterns. Although the structure of FATP1, one of the best understood placental FATPs, has not been fully elucidated, it is proposed to have only one membrane-spanning region and several membrane-associated regions (Lewis *et al.,* 2001). The role of FATP is to enhance fatty acid internalisation through cooperation with acylCoA synthetase. From this, AcylCoA derivatives are created and fatty acid uptake becomes unidirectional as a consequence. Unlike FABPpm, FATP does not have specific preferences for fatty acid uptake.

The cytoplasm of syncytiotrophoblast cells contains intracellular fatty acid binding proteins (FABPs), such as H-FABP (heart), L-FABP (liver), A-FABP (adipose) and E-FABP (epidermal). The roles of these proteins is not yet fully understood. However, they participate in intracellular transport and metabolism of fatty acids — especially in the conversion of the n-3 and n-6 series to their respective derivatives.

Fatty acids can only be transported *via* the microvillous membrane in their non-esterified form. However, due to their hydrophobicity they are not present in the form of fatty acids in the mother's bloodstream. The vast majority of FAs are transported in the form of triglyceride inside very low density lipoprotein fraction or bound to albumins (Auestad *et al.,* 2003). VLDL fractions moving near microvillous membranes are recognised by lipoprotein lipase attached to the membrane surface and hydrolysed to fatty acids which bind with FABPpm, FAT and FATP, and are transported in this form to cytoplasm. Not all fatty acids may be transported to the cell by means of specific conveyors: FABPs. This kind of transport refers mainly to LCPUFAs, which are the first to be disconnected from TG. Other FAs, especially their saturated forms, penetrate into the interior of a cell based on free movement. Irrespective of the cellular transport mechanism, FAs are bound inside the cell by cytoplasmic FABPs occurring in two variants: heart-type H-FABP and liver-type L-FABP. The choice of the cytoplasmic conveyor determines the later metabolism of LCPUFAs. Fatty acids combined with L-FABP undergo esterification and are stored in a cell, or are transported to the basal membrane of syncytiotrophoblast cells and transferred to transport proteins located there, which are the same as those present on the microvillous membrane (FAT and FATP). Other fatty acids combine with H-FABP and are transformed into eicosanoids, as in the case mentioned above, combine with the FAT and FATP of the basal membrane of syncytiotrophoblast cells before entering fetal circulation where they combine with albumin or alpha-fetoprotein (Enke *et al.,* 2008). Owing to the symmetrical distribution of FABP on the microvillous and basal membranes, fatty acids can be transported from maternal to fetal circulation and *vice versa.* In fact, the dynamics of FA transport in both directions is not the same and it is subject to various mechanisms and regulatory factors. For example, the transport of arachidonic acid (AA) to the inside of the cell from maternal circulation and fetal circulation, is an ATP-dependent process, yet its transport across the basal membrane requires Na+ ions in addition to the ATP (Gale *et al.,* 2008).

The regulation of FA transport from the mother to the fetus leads to the emergence of differences in the levels of particular FAs in the blood of the mother and of the fetus. These differences are particularly evident in n-3 and n-6 long-chain polyunsaturated fatty acids (LCPUFAs). The differences stem from a certain preferential relation of placenta towards LCPUFAs involving both their uptake from the mother's bloodstream and transport to the fetal circulation. Studies have shown that the concentration of arachidonic acid (AA) and docosahexaenoic acid (DHA) in the inter-microvillous space is already three to four times higher than in the mother's blood taken from outside the placenta (Schmitters *et al.,* 2008; Cetin *et al.,* 2002; Gauster *et al.,* 2007). This concentration gradient does not result from the release of LCPUFAs from the placenta to maternal circulation but comes into existence because of the lipoprotein lipase discussed above. The enzyme preferentially hydrolyses TG at the 2-position which is most common for unsaturated fatty acids. The released AA and DHA are then transported, also based on principles of priority by FABPpm according to a specified hierarchy DHA > AA > LA > ALA defining the order of transport of the acids across the placental barrier. This hierarchy may change depending on the trimester of pregnancy, the content of these FAs in the placenta and their concentration in maternal and fetal blood. Due to the lack of activity, or very little activity, of placental desaturases there is no biosynthesis of DHA and AA from their precursors — LA and ALA (Cetin & Alvino, 2009) — in the placenta. The source of placental DHA and AA is maternal plasma. Having penetrated into the syncytiotrophoblast, the DHA is further transported to the fetal circulation where it becomes a physiologically important component necessary for the nervous system to function. A part of the placental AA is used in the biosynthesis of prostanoids and leukotrienes, while this what remains, as in the case of DHA, enters fetal circulation. An important factor conditioning the penetration of n-3 and n-6 into the syncytiotrophoblast cells is the concentration of these FAs and, more precisely, their mutual proportions in the inter-microvillous space and in the syncytiotrophoblast cells. The competition for FABP begins as early as in the inter-microvillous space. It results from a particular property of LCPUFA and the law of mass action. The amount of LCPUFA in placental transport is also dependent on the content of trans fatty acid isomers in the maternal blood. These isomers, whose only source is the mother's diet, also compete with LCPUFAs for FABP binding sites, which reduces the placental uptake of LCPUFAs — including those acids that are most important in terms of biology: n-3 and n-6.

Inside the cell, cytosolic fatty acids, both n-3 and n-6, are subject to enzymatic treatment which results in bioactive derivatives belonging to the groups of prostacyclins, prostaglandins, thromboxanes and leukotrienes. The synthesis reactions of the derivatives are catalysed by a complex of oxygenase common to n-3 and n-6. Both groups of fatty acids, while being substrates for the same enzymes, show a mutual inhibitory effect re-

sulting from the competition for an enzyme active site. EPA and AA provide an example of mutual placental inhibition of n-3 and n-6 acids. In the process of the biosynthesis of derivatives, EPA and its metabolites — eicosanoids compete with AA and its derivatives in the placenta for access to cyclooxygenases and lipoxygenases. As a result of this process the placental content of prostanoids and leukotrienes originating from the n-6 group decreases. Alpha-linolenic acid, the precursor of EPA, has similar inhibition properties towards AA and LA transport (Haggarty, 2002; Haggarty, 2004; Burdge & Calder, 2005).

FATTY ACID CHANGES IN PRETERM, SGA AND IUGR INFANTS

According to WHO data, premature birth and subsequent complications caused by irregularities in the course of pregnancy are a growing medical and social problem. Each year approximately 15 million children around the world are born preterm. They require cost-intensive and specialized medical care in the first few weeks of life. Maintaining an optimised supply of FAs during the period of fetal and infant life reduces the risk of IUGR, preterm birth and SGA neonates and, in the long run, reduces the risk of developing diseases such as diabetes, cardiovascular conditions and other chronic conditions later in life (Cetin *et al.,* 2005; de Rooij *et al.,* 2007). If pregnancy takes its proper course, the total plasma fatty acid concentration is higher in the mother than in the fetus (Cetin *et al.,* 2009). This maternal-fetal profile of fatty acids is maintained by specialized placental systems that transport FAs according to a particular hierarchy. In this way a specific FA gradient is created between the blood of the mother and child. As a result of this physiological mechanism the content of DHA and AA increases in cord blood in relation to the levels of their precursors — LA and ALA — in the maternal blood. The maternal-fetal proportions of a number of FAs change in the course of IUGR. The fetal/maternal (F/M) ratio for LA increases, while it decreases for DHA and AA (Cetin *et al.,* 2002). As a result of these disorders there is a quantitative reduction in the amount of DHA and AA available for proper fetal development and for important metabolic processes required for a successfully pregnancy. Changes in the F/M ratio of MCFAs can also be observed during IUGR. Studies have shown that rearrangement of maternal-fetal FAs is already visible in the course of a small degree of pathology, such as late prematurity (weeks 35–37) and the birth of a term SGA child (Bobiński *et al.,* 2013b). The cord blood of premature and SGA infants has also been identified as containing a higher percentage of lauric acid (C12:0), which is one of MCFAs. Analysis of the n-3 and n-6 FA content in cord blood reveals differences when AGA neonates are compared with preterm and SGA neonates. In the range of the n-6 placental FAs of the AGA group, a higher content of Dihomo-γ-linolenic (DGLA, 20:3n-6), eicosatrienic (C20:3n-6) and arachidonic acids can be observed. No statistical differences are observed among the n-3 FAs. This result may indicate that in the case of prematurity and SGA, the n-6 FAs are preferentially transmitted via protein transport systems to fetal circulation. There is a breach of the physiological hierarchy of FA placental transport — DHA > AA > LA > ALA — with n-3 DHA on top, probably resulting in moving AA to the top of the hierarchy. The proof of these changes in preferences in the placental transport of DHA is the variation in the relationships between DHA concentrations in cord blood and DHA concentrations in maternal blood (DHA_F/DHA_M) between the groups of AGA, preterm (weeks 35–37) and SGA neonates. The algebraic value of these relations is approximately 100% lower in the group of mothers whose children were born prematurely, and the group of mothers with SGA children, than it is in the AGA group (Bobiński *et al.,* 2013b). This means that the amount of DHA transported across the placenta is smaller in preterm and small-for-gestational-age neonates than in AGA ones. Consequently, a lower amount of DHA is available for fetal development processes, including that of creating the nervous system, for which DHA is an essential polyunsaturated fatty acid. Changes in the maternal-placental relationships of FA content also apply to AA, LA and ALA, which suggests that the placental transport of fatty acids that are essential from the biological point of view changes in the course of slight prematurity or hypotrophy.

RECOMMENDATIONS

One of the basic preconditions for the proper development of human beings is that an appropriate FA profile is provided to the organism in the intrauterine development, neonatal and infant periods. There are a number of research papers containing dietary recommendations for n-3 and n-6 during pregnancy and lactation (Haggarty, 2004; FAO, 2010; Duttaroy 2009b). Analysis of the range of FAs shows that MCFAs play an important role in fetal development. Changes in the levels of these acids can be observed in cases of IUGR, prematurity and SGA in pregnancy diet (Pardi *et al.,* 2002), maternal blood (Cetin *et al.,* 2002; Bobiński *et al.,* 2013b), cord blood (Cetin *et al.,* 2002, Bobiński *et al.,* 2013b) and breast milk (Nasser *et al.,* 2010; Bobiński *et al.,* 2013a). Physiologically, these FAs fulfil many significant energetic and metabolic functions, which are especially important for the fetus and neonate. In the digestive system of an enzymatically underdeveloped child, following birth TGs containing FAs with the carbon number C10-C12 are preferentially degraded by pancreatic lipase and absorbed directly into the blood circulation — omitting the incorporation of FAs into chylomicrons (Schmeits *et al.,* 1999). The bactericidal effect they exert on microorganisms in the digestive tract is also an important aspect. The specific construction of medium-chain fatty acids allows for relatively easy penetration of MCFAs into the cell in an undissociated form where they then undergo dissociation. Dissociation deteriorates the delicate pH balance inside bacteria. To maintain a neutral pH, a bacterial cell begins to consume large quantities of ATP to preserve the proper acid-base balance. As a result, excessive demand for ATP affects the limitation and — finally — the inhibition of other metabolic processes of bacteria (e.g. protein synthesis), which eventually leads to its necrosis (Rickie, 2003). The case described has been observed mainly in the intestines of both humans and animals, where MCFAs impeded the growth of gram-positive and gram-negative bacteria (Nakai & Siebert, 2002). It has also been observed that antibacterial activity can be reduced along with the extension of the MCFA carbon chain. The inhibitory properties of MCFAs with regard to *Clostridium, Salmonella, Escherichia* and *Helicobacter* are now reasonably well documented (Nakai & Siebert, 2002; Mauronek *et al.,* 2003; Skrivanowa *et al.,* 2006; Szewczyk & Hanczakowska, 2010). In the case of

the latter bacteria high activity is demonstrated mainly by lauric acid and medium-chain monoacylglycerols.

MCFAs perform another important role in acylation. This is especially true in the case of the myristoylation of proteins and in the conversion of essential unsaturated fatty acids of alpha-linolenic acid (ALA, C18:3n-3) and linoleic acid (LA, C18:2n-6) to their physiologically most important derivatives: docosahexaenoic acid (DHA, C22:6n-3) and arachidonic acid (AA, 20:4n-6) (Legrand *et al.,* 2002) (Fig. 4). Taking into account the physiological and biochemical role of MCFAs, recommended norms for their consumption by pregnant women along with norms for the enrichment of breast-milk substitute in IUGR, SGA and preterm cases should be elaborated. Studies have established that the daily intake of capric acid, lauric acid and myristic acid should not be less than 1.05 g/day, 1.45 g/day and 4.8 g/day (Bobiński *et al.,* 2015a) respectively. Clarification of the optimum amount of MCFAs for the mother and for the fetus will require further research on a larger population of pregnant women.

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