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SYMPOSIUM REVIEW

Long chain fatty acids and dietary fats in fetal nutrition

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Long chain polyunsaturated fatty acids are essential nutrients for a healthy diet. The different kinds consumed by the mother during gestation and lactation may influence pregnancy, fetal and also neonatal outcome. The amount of fatty acids transferred from mother to fetus depends not only on maternal metabolism but also on placental function, i.e. by the uptake, metabolism and then transfer of fatty acids to the fetus. The third trimester of gestation is characterized by an increase of long chain polyunsaturated fatty acids in the fetal circulation, in particular docosahexaenoic acid, especially to support brain growth and visual development. These mechanisms may be altered in pathological conditions, such as intrauterine growth restriction and diabetes, when maternal and fetal plasma levels of long chain polyunsaturated fatty acids undergo significant changes. The aim of this review is to describe the maternal and placental factors involved in determining fetal fatty acid availability and metabolism, focusing on the specific role of long chain polyunsaturated fatty acids in normal and pathological pregnancies.

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Abbreviations ARA, arachidonic acid; αLA, α-linolenic acid; CNS, central nervous system; DHA, docosahexaenoic acid; EFAs, essential fatty acids; EL, endothelial lipase; EPA, eicosapentaenoic acid; FAs, fatty acids; FABP, fatty acid binding protein; FFA, free fatty acid; FAT, fatty acid translocase; GDM, gestational diabetes mellitus; IUGR, intrauterine growth restriction; LA, linoleic acid; LC-PUFAs, long chain polyunsaturated fatty acids; LPL, lipoprotein lipase; PE, preeclampsia; PPD, post-partum depression; PUFAs, polyunsaturated fatty acids; Th1 and Th2, Thelper 1 and 2.

Fatty acids (FAs), together with glucose, lactate and amino acids, represent essential nutrients during intrauterine life. Amongst fatty acids, polyunsaturated fatty acids (PUFAs) are of particular relevance because of their numerous physiological functions (metabolic, energetic and structural) and for the potential influence of their changes on some pathological conditions.

In particular, docosahexaenoic acid (DHA) is an ω-3 long chain polyunsaturated fatty acid (LC-PUFA) that has been widely investigated for its critical importance on fetal growth and especially on CNS development.

This review summarizes maternal and placental metabolism of fatty acids with a specific focus on PUFAs, the mechanisms involved in their transfer to the fetus, their changes in pathological conditions, and their role in fetal neurodevelopment.

Maternal fatty acids: changes with gestation

Fats are part of a balanced and wholesome diet but the type and total amount consumed is important to maintain the state of health. The recommended fat intake for adults ranges between 20 and 35% of total calories (*Dietary guidelines for Americans, 2005*; U.S. Department of Health).

The most important lipids usually introduced with diet are triglycerides and to a lesser extent phospholipids and cholesterol esters. These are complex molecules that once introduced into the organism cannot be wholly absorbed by the intestine but they have to be broken into simpler molecules by specific pancreatic enzymes.

According to the number of double bonds in the hydrocarbon chain, fatty acids can be classified as saturated and unsaturated, with no, or one or more double bonds, respectively. LC-PUFAs (18 or more carbons) can be

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further distinguished as two key families, ω-3 and ω-6 depending on the position of the first double bond in the hydrocarbon chain. They have many distinct functions: energetic, metabolic and structural.

Among polyunsaturated fatty acids, linoleic (LA; 18:2 ω-6) and α-linolenic (αLA; 18:3 ω-3) acids are called 'essential fatty acids' (EFAs) because they cannot be synthesized endogenously but they have to be introduced with food, in particular by consumption of vegetable oils.

EFAs are converted into their main metabolites which are able to exert the full range of biological actions (Burdge & Calder, 2005). Derivatives of αLA are represented by DHA (22:6 ω-3), necessary for brain growth and development (Innis, 2005) and eicosapentaenoic acid (EPA; 20:5 ω-3), the precursor of series-3 prostaglandins which inhibit platelet aggregation. LA is converted to arachidonic acid (ARA; 20:4 ω-6), the main precursor of prostaglandins, thromboxanes and leukotrienes, fundamental for immune responses. DHA, EPA and ARA may also be introduced with diet: ω-3 are mainly present in fish, shellfish, and sea mammals and are scarce in land animals and plants, whereas ω-6 mainly derive from vegetable oils (Bézard *et al.* 1994; Innis, 2003).

The Δ5–Δ6 enzymatic chain promotes the conversion of ARA from LA, and EPA from αLA. Due to a competition mechanism, EPA and DHA are produced more efficiently than ARA in an abundance of αLA. For this reason, higher intakes of ω-3 are recommended for many pathological conditions (heart diseases, atherosis and autoimmune diseases) in order to reduce the production of prostanoids derived from ARA, such as prostaglandin E_2 and thromboxane A_2.

The mother modifies her metabolism from the beginning of pregnancy in order to support the nutritional needs of the feto-placental unit (Fig. 1) (Cetin *et al.* 2005). The first trimester of pregnancy can be considered an anabolic period during which the mother increases her net body weight through hyperphagia and substance storing in adipose tissue, also under conditions of malnutrition (Prentice & Golberg 2000; Herrera 2002). Fat storage is facilitated by increasing the insulin responsiveness of adipose tissue which reduces lipoprotein lipase activity.

In the third trimester of pregnancy the fetus intensifies its nutrient demands to support exponential tissue growth, so maternal lipid metabolism switches to a catabolic condition. In this stage, even short fasting periods are associated with a condition defined as accelerated starvation, during which the pregnant woman makes available to the fetal–placental unit large quantities of nutrients (Fig. 2) (Felig *et al.* 1970).

Adipose tissue lipolytic activity increases due to a reduction in insulin sensitivity, under the hormonal control of progesterone, cortisol, prolactin and leptin (Cousins, 1991; Catov *et al.* 2007). High circulating oestrogens determine a decrease in extra-hepatic lipoprotein lipase (LPL) activity (Alvarez *et al.* 1996), whereas the intestinal absorption of dietary fats increases (Argiles & Herrera, 1989; Herrera, 2002). All these events result in elevations of free fatty acids (FFAs) and glycerol plasma levels taken up by the liver for the synthesis of Very Low Density Lipoprotein (VLDL), rich in triglycerides, quickly released into the circulation. Therefore, the hyper-triglyceridaemia that characterizes this phase of gestation is mainly due to an increase in VLDL production and a decrease in its peripheral clearance (Alvarez *et al.* 1996; Herrera, 2002).

During the last weeks of gestation, mainly under fasting conditions, FFAs and glycerol released from the adipose tissue can be used for ketone bodies synthesis (Zorzano *et al.* 1986; Herrera 2002). Ketone bodies and FFAs, similarly to glucose, may easily cross the placenta to sustain the augmented fetal metabolism. However, this is not very relevant in quantitative terms, since fatty acids are mainly

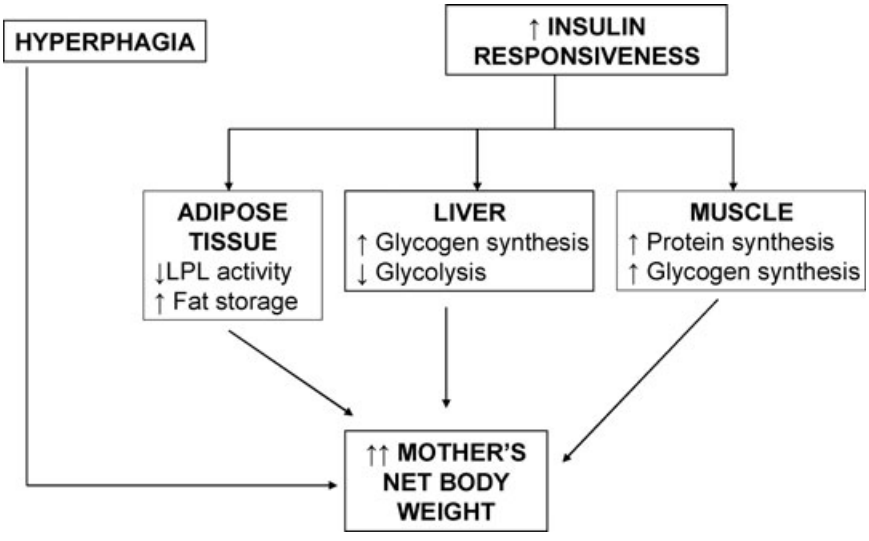

Figure 1. Anabolic maternal metabolism in the first trimester of pregnancy
In this phase, the mother stores lipids, proteins and carbohydrates thanks to the enhanced insulin sensitivity and hyperphagia.

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provided to the fetal circulation by placental transport and eventually by elaboration of lipoproteins (Wittmaack *et al.* 1995; Herrera 2002).

We previously reported an increment in proportion of total saturated fatty acids during normal pregnancy, with a decline in ω-6 probably as a result of a decline in the percentage of ARA, with a stable proportion of LA, the most abundant ω-6 fatty acid in maternal plasma. Concerning ω-3, their total amount is stable during gestation, with an increment in percentage αLA and a reduction in EPA and DHA (Herrera *et al.* 2004).

Cholesterol and triglyceride levels increase during pregnancy, with an increment in FFAs mostly near delivery (Herrera *et al.* 2004).

After delivery, LC-PUFA content in circulating lipoproteins shows a greater decline in the triglyceride fraction than in phospholipids or esterified cholesterol. Plasma FFAs fall to pre-pregnancy levels within 3 days and triglycerides in 2 weeks, although this also depends on maternal lactation, being more rapid in women that establish breast feeding (Montelongo *et al.* 1992).

Placental transfer and fetal levels of fatty acids

During intrauterine life the fetus is dependant for its growth and development on the nutrients provided by the mother. The amount of substrates reaching the placenta strictly depends on maternal diet and metabolism. However, the placenta plays a major role since its transfer ability and metabolism together determine the amount of nutrients in the fetal circulation (Cetin *et al.* 2005).

FAs are taken up by the placenta from the maternal circulation as FFAs or as maternal lipoproteins. FAs incorporated in maternal lipoproteins are released by placental lipoprotein lipases. FFAs may be transferred to the fetus by simple diffusion because the FFA concentration gradient between the mother and the fetus increases steadily during pregnancy (Benassayag *et al.* 1999) or, more importantly, through transport proteins located on the microvillus or basal membranes of trophoblast cells and on endothelial membranes of fetal capillaries (Fig. 3).

A number of studies suggest that the placenta modulates the fatty acids supply for its own metabolism and also that of the fetus. Indeed, leptin produced by the placenta and secreted both in the maternal and fetal circulations stimulates lipolysis (Masuzaki *et al.* 1997; Hoggard *et al.* 2001).

Maternal lipoproteins rich in triglycerides do not directly cross the placenta but they require hydrolysis by placental lipoprotein lipase, so that the major source of FAs in the fetal circulation is represented by free fatty acids (Herrera *et al.* 2006). FFAs can cross the lipid bilayers by simple diffusion or connecting to specific binding proteins or albumin (Herrera *et al.* 2006).

Generally speaking, fetal fatty acids are correlated to the maternal levels, with significantly lower total levels in the fetal than in the maternal circulation (Cetin *et al.* 2002). However, numerous studies have proved that the FA profile is different in the fetal compared with the maternal circulation, with higher proportions of LC-PUFAs and a lower percentage of their precursors

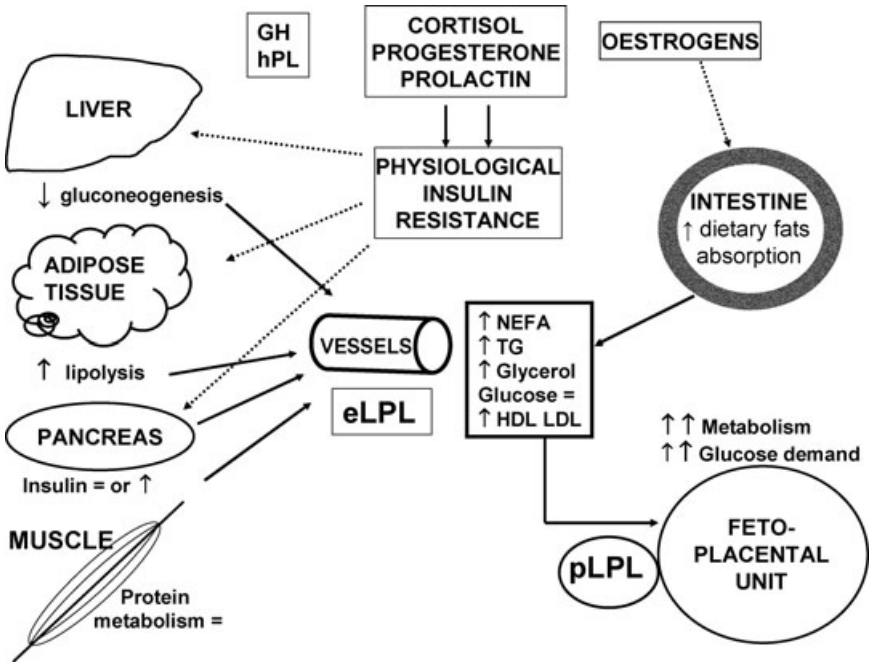

Figure 2. Catabolic maternal metabolism in the third trimester of pregnancy: availability of nutrients to sustain fetal growth
eLPL: endothelial lipoprotein lipase; pLPL placental lipoprotein lipase.

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LA and αLA (Crawford *et al.* 1976). This phenomenon is called 'biomagnification' and seems to be related to the ability of the placenta or the fetus to increase LC-PUFA percentages in fetal blood in order to support central nervous system development. However, the biochemical mechanisms responsible for this are not yet completely clarified. In particular Δ5 and Δ6 desaturase activities are very low in placental tissue (Llanos *et al.* 2005). Fetal ability to desaturate and elongate fatty acids was demonstrated for LA → ARA conversion, but this capability is less efficient for DHA (Szitanyi *et al.* 1999).

Biomagnification of ARA and DHA in fetal plasma is therefore probably due to the placental ability to preferentially transfer DHA and then ARA, ALA and LA into fetal circulation as demonstrated by *in vitro* and *in vivo*, and by stable isotope experiments (Ruyle *et al.* 1990; Haggarty *et al.* 1999; Larqué *et al.* 2003).

Several FA transfer proteins have been identified in the placenta:

FABPs: different isoforms of these fatty acid binding proteins have been recognized in the placenta. FABPpm is located only on the membrane-facing maternal circulation of trophoblast cells and preferentially binds LC-PUFA (Campbell *et al.* 1998*b*) and Liver-FABP (L-FABP) located in the cytoplasm (Campbell *et al.* 1998*a*).

FAT/CD36 (FA translocase): this is an integral membrane protein placed in both the placental membranes involved not only in lipid metabolism but also in angiogenesis and inflammation (Campbell *et al.* 1998*a*).

FATPs (FA transporter proteins): integral trans-membrane proteins located on both trophoblast membranes (Campbell *et al.* 1998*a*).

The location of FAT and FATP on both sides of trophoblast cells and their lack of specificity for a particular type of FFA allows their transport to occur bidirectionally from mother to fetus and vice versa. However, for its exclusive location on the maternal side and its preference for LC-PUFAs, FABPpm seems to be implied in their sequestration in the placenta. (Campbell *et al.* 1998*a*; DuttaRoy, 2000, 2008).

Once in the placenta, FAs are in part oxidized in mitochondria to produce energy. Moreover, they are incorporated into phospholipids while a certain proportion of ARA is converted into prostaglandins by cyclooxygenases. The remaining FAs are elongated, desaturated and then released into the fetal circulation. A different fetal blood FA profile is observed, with proportionally higher amounts of LC-PUFAs in comparison with those present in the maternal circulation.

The simultaneous evaluation of lipid and fatty acid profile in mother and fetus during gestation is very difficult under normal conditions. While it is possible to describe this profile at different gestational ages in fetuses that are born prematurely, this event could in itself condition or be conditioned by an alteration in lipid profile (Olsen, 2004).

A few years ago, we described the fetal fatty acid profile in the second half of pregnancy using fetal blood sampling performed *in utero* to evaluate fetal karyotype (Cetin *et al.* 2002). In that study, we reported few changes occurring with gestation, namely an increase in saturated (mainly palmitic acid) and polyunsaturated fatty acids, and a decrease in oleic and consequently in the percentage of mono-unsaturated fatty acids. No differences were observed in the profile of LC-PUFAs during gestation.

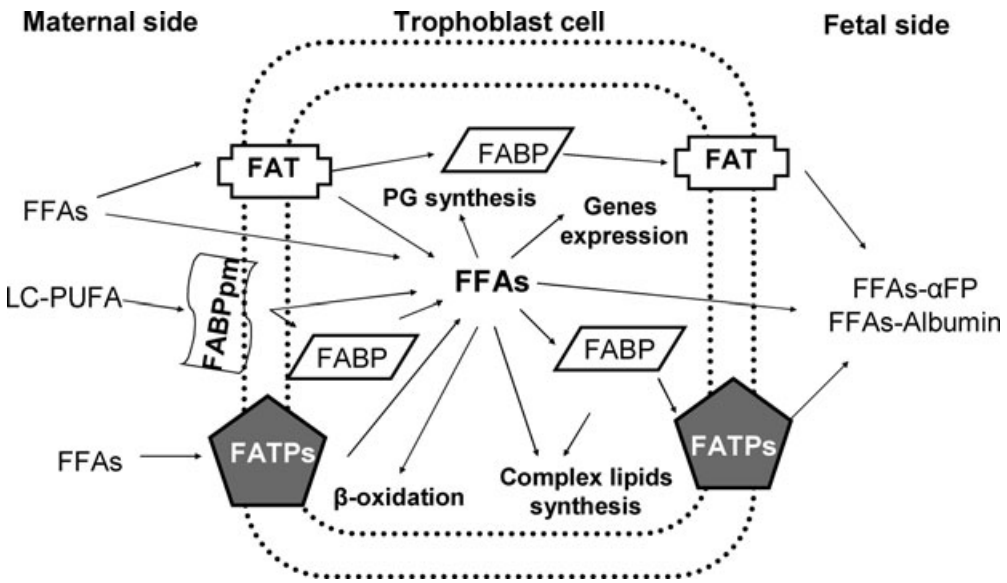

Figure 3. Schematic view of fatty acid transport proteins in the human placenta

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Table 1. Effects of ω-3 on fetal central nervous system development

Smithers *et al.* 2008	Increased visual acuity	(*) VEP at 4 months: high-DHA fetuses had 1.4 cpd higher than controls ($P = 0.025$)
Cheruku *et al.* 2002	Favoured mature neonatal sleep state	($) Infants of high-DHA mothers had a significantly lower AS/QS ratio ($P < 0.05$) and < AS than infants of low-DHA mothers ($P < 0.05$)
Gale *et al.* 2008	Reduced hyperactivity	(°) Reduced risk of hyperactivity in fetuses of FO supplemented mothers (OR = 0.34 95% CI 0.15–0.78)
Helland *et al.* 2003	Higher IQ at 4 years of age	(§) Mean IQ 106 *vs.* 102 ($P < 0.05$)

(*)VEP: visual evoked potential; cpd: cycle per degree
($) AS: active sleep; QS :quiet sleep
(°) FO: fish oil, OR: odd ratio
(§) Scores on the Mental Processing Composite of the K-ABC (Kaufman Assessment Battery for Children) for children whose mothers had taken cod liver *vs.* corn oil during pregnancy and lactation.

Table 2. Effects of ω-3 on pregnancy and fetal outcome

Szajewska *et al*. 2006	Prolong gestation	Mean 1.57 days (95% CI: 0.35, 2.78)
	Increase of birth weight	Mean 47 or 54 g
Horvath *et al*. 2007	Prevent preterm birth (< 34 weeks) in high risk patients	RR 0.39 (95% CI 0.18, 0.84)
Enke *et al*. 2008	Influence fetal immune response	DHA reduces inflammatory cytokines
Hibbeln, 2002	Deficiency increases risk of post-partum depression (PPD)	Prevalence of PPD is higher in countries with lower consumption of seafood ($r = -0.81$ $P < 0.0001$) and lower concentration of DHA in mother's milk ($r = -0.84$; $P < 0.0001$).
Weisinger *et al.* 2001	Deficiency increases blood pressure	Rats fed with a deficient ω-3 diet had a higher blood pressure than controls ($P < 0.05$)

RR: risk ratio

Relevance of fatty acids in fetal nutrition

The third trimester of pregnancy is characterized by massive fetal growth and consequently a high demand of nutrients by the fetus. During this period and through the early weeks of life it has been estimated that the fetus needs approximately 50 mg/kg/day of ω-3 and 400 mg/kg/day of ω-6 (Clandinin *et al.* 1980, 1981). The brain is the organ that most of all rapidly incorporates LC-PUFAs for its development. In particular, DHA is selectively incorporated into fetal brain and retina phospholipids more than 10 times faster than LA and αLA, while ARA is mainly used in postnatal life.

DHA confers a high degree of fluidity and flexibility to neural and endothelial membranes of the central nervous system. DHA is involved in neurotransmission, regulates ion-channel activity and gene expression and can be metabolized in neuroprotective metabolites (Innis, 2007*a*). Recent studies on rats suggest that deficiency of brain ω-3 provokes a reduction of neuron size and dendritic arborization (Ahmad *et al.* 2002). In rhesus monkeys, however, a deficient ω-3 diet reduces rod photo-transduction sensitivity and delays rod recovery but does not influence cone activity (Jeffrey & Neuringer, 2009). In a previous study the same group noticed that in monkeys ω-3 FA deficiency also influences fluid intake and output without affecting serum electrolyte levels; the exact mechanisms of these changes still have to be elucidated (Reisbick *et al.* 1990).

Considering the main role of DHA for brain and retina function and because the amount of FAs in the fetal circulation largely depends on the FA composition of maternal blood, many studies have investigated the effects on brain activity with increasing maternal dietary intake of ω-3 LC-PUFA during pregnancy and lactation. These studies have proved that supplementation has many favourable effects: increased visual acuity (Smithers *et al.* 2008), more mature neonatal sleep state (Cheruku *et al.* 2002), reduced hyperactivity (Gale *et al.* 2008) and enhanced cognitive functions and attention. It is still not known if these benefits persist to childhood and adult life, but in a trial with 4 years follow up, children born to supplemented mothers seem to have a higher IQ than controls (Helland *et al.* 2003) (Table 1). Further studies are required to further understand the role of LC-PUFAs in brain development but we have to consider that neuronal processes are complex and multifactorial so that confounding factors such as maternal baseline intake of LC-PUFAs, socioeconomic status or education may influence the results.

LC-PUFAs are essential components of membrane phospholipids not only in CNS but also in other organs and tissues and so the potential benefits of their

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supplementation on pregnancy outcome have been widely investigated in numerous studies (Table 2). In particular, a recent meta-analysis has shown that supplementation with ω-3 prolongs gestation by an average value of 1.6–2.6 days, with a concomitant small increase in birth weight. Moreover, it prevents preterm birth before 34 weeks of gestation mainly in high risk pregnancies (Szajewska *et al.* 2006). This evidence could be explained by the influence of high concentrations of ω-3 on the production of prostaglandin involved in the initiation of labour.

A recent study has correlated LC-PUFA levels in the uterus with the immune phenotype in childhood due to their ability to influence Th1 and Th2 balance. In particular ARA enhances the inflammatory process while DHA decreases inflammatory cytokines; consequently DHA supplementation seems to have a potential role in preventing future allergies (Enke *et al.* 2008).

Among many effects of LC-PUFAs on fetal and pregnancy outcomes, they seem to have an influence also on maternal depression. Epidemiological studies have shown that the prevalence of post-partum depression is higher in countries with low ω-3 intake than in those with highest intake (Hibbeln, 2002). In particular, post-partum depression (PPD) seems to be related to a higher ω-6/ω-3 ratio (De Vriese *et al.* 2003). The mechanism underlying this observation could be the physiological reduction of DHA contents in maternal brain lipids in the late stage of pregnancy and during lactation. This physiological event, associated with the evidence that pregnant women with a current episode of major depression seem to have lower ω-3 PUFA levels than healthy controls, seems to predispose these patients to an elevated risk of developing PPD (Rees *et al.* 2009). Few studies and with different dosages have investigated the role of ω-3 supplementation on PPD incidence with discordant results (Llorente *et al.* 2003; Freeman *et al.* 2006).

Besides the positive role of a suitable maternal diet with a sufficient intake of LC-PUFAs, it is important to underline that an unbalanced maternal diet may also have potential dramatic consequences on the developing fetus. In rats, abnormal maternal consumption of saturated fatty acids may permanently alter fetal lipid and glucose metabolism in the offspring, increasing the risk for cardiovascular disease in adult life (Siemelink *et al.* 2002; Chechi & Cheema 2006; Chechi *et al.* 2009). Hypertension in particular seems to be related to an excessive intake of saturated FAs or to an inadequate intake of LC-PUFAs in the perinatal period (Weisinger *et al.* 2001; Khan *et al.* 2005).

Fatty acid changes in intrauterine growth restriction and diabetes

Fetal growth depends on a combination of different factors: endocrine maternal state, nutritional maternal environment and genetic potential of the fetus. The alteration of one or more of these factors can lead to a modification in the fetal growth trajectory. Intrauterine growth restriction (IUGR) results from insufficient growth of the fetus, while gestational diabetes is associated with increased nutrient availability and fetal overgrowth.

IUGR, which affects approximately 7–15% of pregnancies, is a condition characterized by an inadequate ability of the placenta to provide nutrients and oxygen to the growing conceptus (Cetin *et al.* 2005; Cetin & Alvino, 2009). IUGR represents one of the principal causes of perinatal morbidity and mortality and is also associated with cardiovascular disease and glucose intolerance in adult life (De Rooij *et al.* 2007).

Many studies have proved that the placenta of IUGR fetuses has a specific phenotype characterized by altered metabolism and decreased nutrient transport. In particular, supply of amino acids is reduced with an increased maternal–fetal gradient of glucose (Sibley *et al.* 2005).

In normal pregnancy, total plasma fatty acid concentrations are significantly higher in mothers than in fetuses with differences in the relative amounts of some fatty acids. Although the total amount of fatty acids is unchanged in IUGR (Cetin *et al.* 2002), we have reported changes in the LC-PUFA fetal/maternal relationship in IUGR at the time of fetal blood sampling, with significantly higher F/M ratios for LA and significantly lower for DHA and ARA. We also demonstrated that fetuses with IUGR have a lower proportion of ARA and DHA relative to their precursors LA and αLA in comparison with control infants of similar gestational age. These data can explain the high susceptibility of IUGR infants to brain and vascular damage.

In a more recent study (Alvino *et al.* 2008) we have evaluated the maternal and fetal blood FA profile in pregnancies complicated by IUGR with or without pre-eclampsia.

Pre-eclampsia is a syndrome typically correlated with placental insufficiency beginning with a shallow trophoblast invasion of spiral arteries similar to the pathogenesis of IUGR (Pardi *et al.* 2002). However, this condition is also characterized by an escalation in inflammatory response to ischaemic damage that succeeds in involving different areas of the maternal circulation. The role of fatty acids, particularly EPA (ω-3) and ARA (ω-6), which are precursors of prostanoids, could be very important in limiting (ω-3 prostanoids) or enhancing (ω-6 prostanoids) this inflammatory condition (Innis, 2005).

We reported a lower ARA/LA ratio in IUGR compared to normal fetuses (Alvino *et al.* 2008). Moreover, IUGR fetuses in pregnancies complicated with pre-eclampsia (IUGR-PE) showed a lower percentage of ARA in venous plasma. Their mothers had significantly higher

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concentrations of triglycerides in comparison with IUGR only and normal mothers and this could represent a risk factor for hypertensive disorders and development of the metabolic syndrome in later life (Carpenter, 2007).

Both in IUGR and IUGR-PE mothers we reported higher concentrations of FFAs associated with higher fetal concentrations. Our group previously demonstrated a higher expression of LPL (lipoprotein lipase) and EL (endothelial lipase) genes in IUGR placentas that could be associated with these results but also with the different distribution of fatty acids in these pathological conditions (Tabano *et al.* 2006; Gauster *et al.* 2007).

The opposite phenotype of IUGR is represented by the fetal overgrowth that characterizes pregnancies complicated by diabetes types I and II, and GDM (gestational diabetes mellitus) (Catalano *et al.* 2007). Intrauterine exposure to these pathologies is a significant determinant of the development of obesity, dyslipidaemia and early onset of type 2 diabetes mellitus in the offspring (Schaefer-Graf *et al.* 2005; Harder *et al.* 2007). It is known that in these conditions there is an altered placental transport activity with an increase in glucose and amino acid transfer (Jansson *et al.* 2006). Moreover, since diabetic women have higher plasma levels of triglycerides-lipoproteins and FFAs than healthy controls, lipid transfer is also increased by the rising of the maternal–fetal concentration gradient (Hollingsworth *et al.* 1982; Montelongo *et al.* 1992). Recent evidence showed that placenta LPL activity is increased by 39% in Insulin Dependent Diabetes Mellitus (IDDM), but not in GDM patients, while the expression of L-FABP (cytoplasmic FA binding protein) is increased both in IDDM and GDM by 112% and 69%, respectively (Magnusson *et al.* 2004). In diabetic pregnancy, a large proportion of lipids that cross the placenta are stored directly in the placental unit while the remainder are released into the fetal circulation and contribute to fetal fat deposition together with glucose (Magnusson *et al.* 2004).

GDM pregnancies are also associated with higher placental/fetal weight ratios (Taricco *et al.* 2003) reflecting a greater layer of exchange and/or a major density of nutrient transporters. This leads to higher availability of nutrients for the fetus with more tissue deposition, particularly fat. Moreover, the quality of fatty acids that reach the fetus could be different, because of the great enhancement of lipolysis observed in GDM mothers affecting the fatty acids pattern (Wijendran *et al.* 1999; Thomas *et al.* 2004).

In non-pregnant women, diabetes determines a reduced synthesis of ARA and DHA probably due to an impaired activity of $\Delta 5$ and $\Delta 6$ desaturases (Brenner *et al.* 2000). Although this evidence has not been found in patients with GDM (Thomas *et al.* 2004), both diabetic and GDM patients show depressed levels of ARA and DHA in red blood cell phospholipids (Wijendran *et al.* 1999).

We recently reported lower percentages of both ARA and DHA in umbilical arterial plasma but not in the umbilical vein of GDM neonates (Ortega-Senovilla *et al.* 2009) (Fig. 4). These data suggest that a lower

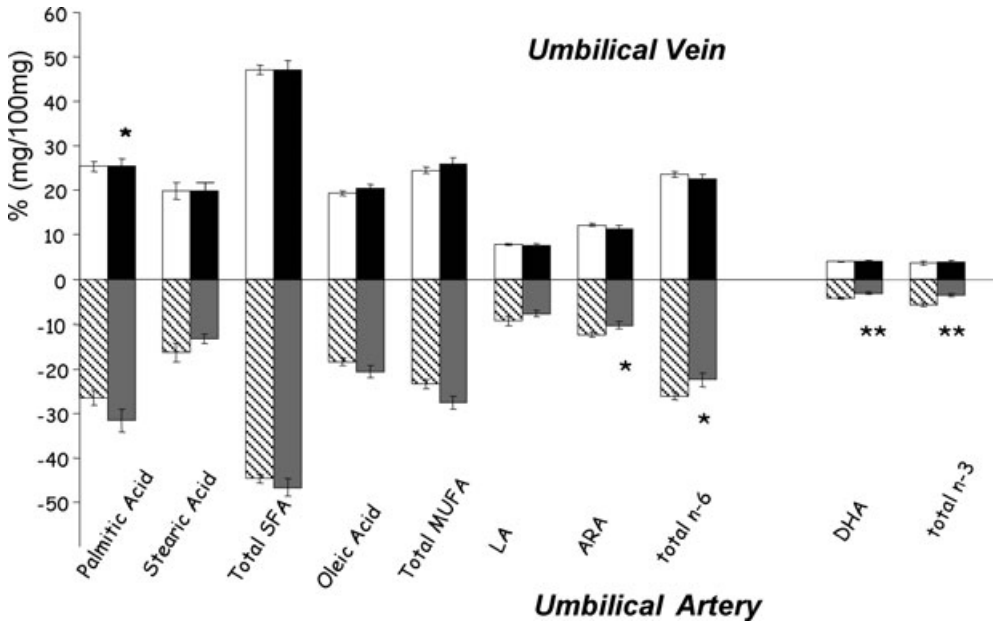

Figure 4. Fatty acid profile in arterial and venous plasma of AGA (adequate for gestational age) and GDM fetuses

$^{*}P < 0.05$, $^{**}P < 0.01$ ANOVA and Tukey's test between u.v. (umbilical vein) and u.a. (umbilical artery). Open columns, u.v. AGA; shaded columns, u.a. AGA; filled columns, u.v. GDM; grey columns, u.a. GDM. SFA, saturated fatty acids; MUFA, monounsaturated fatty acids. Data adapted from Ortega-Senovilla *et al.* (2009).

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concentration of LC-PUFAs in neonates of GDM mothers seems to be due to altered fetal metabolism rather than limited placental transfer. This finding could have potential implications for fetal and postnatal growth that need to be investigated.

There are also important metabolic changes that characterize pregnancies complicated by maternal obesity but with normal glucose tolerance. Maternal obesity is associated with a higher risk of complications like pre-eclampsia, GDM, fetal anomalies and high birth weight (King, 2006). In obese women, the physiological metabolic adjustments are amplified: insulin sensitivity is 40% lower with a consequent increase in plasma glucose, amino acids and plasma FFAs (King, 2006). Therefore obesity, like GDM, leads to an excess of available nutrients for the fetus, heavily influencing its growth and development.

Conclusions and recommendations

In conclusion, it is clear that LC-PUFA intake may influence fetal, maternal and child health. It is therefore advisable that pregnant and lactating women aim to achieve an average intake of at least 200 mg/day of DHA to achieve a desirable outcome (Koletzko *et al.* 2007). For this purpose, women should consume oily fish two times a week during pregnancy, because of its beneficial effects on vascular function and on the developing fetal brain and retina. Only Carlson *et al.* (1996) reported that supplementation of premature infants with marine oils can adversely affect neonatal growth because of an altered balance of ω-3 (EPA) and ω-6 (reduction of ARA $\rightarrow$ prostanoids $\rightarrow$ growth factors), but usually the supply of ARA with the diet and from maternal adipose tissue is sufficient to maintain a correct ω-3/ω-6 ratio. The beneficial effect of DHA on prolonging gestation and consequently fetal weight is very consistent in different studies (Smuts *et al.* 2003; Olsen *et al.* 2007).

Of note, since marine fish may contain large quantities of dangerous contaminants such as polychlorinated biphenols, dioxins and mercurial derivatives (Grandjean & Weihe, 2003) women should be advised to consume non-predator fish with a lower content of contaminants (Koletzko *et al.* 2008).

Moreover, dietary fat intake during pregnancy and lactation, as a proportion of total energy intake, should be the same as that recommended for the general population.

However, further research is needed in order to better characterize the mechanisms regulating the placental transfer of long chain fatty acids.

Finally, maternal intake of dietary fats in the peri-conceptional period should be investigated in future studies in order to determine a potential role in implantation and in early embryo development.

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