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Implications of Dietary Fatty Acids During Pregnancy on Placental, Fetal and Postnatal Development—A Review

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During pregnancy, the mother adapts her metabolism to support the continuous draining of substrates by the fetus. Her increase in net body weight (free of the conceptus) corresponds to the accumulation of fat depots during the first two-thirds of gestation, switching to an accelerated breakdown of these during the last trimester. Under fasting conditions, adipose tissue lipolytic activity is highly enhanced, and its products, free fatty acids (FFA) and glycerol, are mainly driven to maternal liver, where FFA are converted to ketone bodies and glycerol to glucose, which easily cross the placenta and sustain fetal metabolism. Lipolytic products reaching maternal liver are also used for triglyceride synthesis that are released in turn to the circulation, where together with an enhanced transfer of triglycerides among the different lipoprotein fractions, and a decrease in extrahepatic lipoprotein lipase activity, increase the content of triglycerides in all the lipoprotein fractions. Long chain polyunsaturated fatty acids (LCPUFA) circulate in maternal plasma associated to lipoprotein triglycerides, and in a minor proportion in the form of FFA. Despite the lack of a direct placental transfer of triglycerides, diffusion of their fatty acids to the fetus is ensured by means of lipoprotein receptors, lipoprotein lipase activity and intracellular lipase activities in the placenta. Maternal plasma FFA are also an important source of LCPUFA to the fetus, and their placental uptake occurs via a selective process of facilitated membrane translocation involving a plasma membrane fatty acid-binding protein. This mechanism together with a selective cellular metabolism determine the actual rate of placental transfer and its selectivity, resulting even in an enrichment of certain LCPUFA in fetal circulation as compared to maternal. The degree to which the fetus is capable of fatty acid desaturation and elongation is not clear, although both term and preterm infants can synthesize LCPUFA from parental essential fatty acids. Nutritional status of the mother during gestation is related to fetal growth, and excessive dietary intake of certain LCPUFA has inhibitory effects on Δ-5- and Δ-6-desaturases. This inhibition causes major declines in arachidonic acid levels, as directly found in pregnant and lactating rats fed a fish oil-rich diet as compared to olive oil. An excess in dietary PUFA may also enhance peroxidation and reduce antioxidant capacity. Thus, since benefit to risks of modifying maternal fat intake in pregnancy and lactation are not yet completely established, additional studies are needed before recommendations to increase LCPUFA intake in pregnancy are made.
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INTRODUCTION

Fetal metabolism, and consequently fetal growth, directly depend on the nutrients crossing the placenta, and therefore, the mother must adapt her metabolism in order to support this continuous draining of substrates. Glucose, which is the principal carbohydrate crossing the placenta, is transported by facilitative diffusion according to a concentration-dependent kinetics, whereas amino acids are transported through energy-dependent processes, via selective transporters. However, knowledge about placental transport of lipids is still scant. Maternal triglycerides are not transported intact, since the mechanisms in the placenta only allow transfer of their esterified fatty acids to the fetus, which together with the transport of unesterified fatty acids from maternal circulation, fulfill the requirements of essential fatty acids by the developing fetus. Dietary deviations in maternal fatty acids intake throughout pregnancy may affect the nature of fatty acids crossing the placenta, having consequences to fetal neuronal maturation and postnatal development. Strategies have been proposed to modify maternal intake of certain essential fatty acids to warrant their availability to the fetus, but an excess of certain fatty acids may impair the availability of others, with undesirable consequences to the newborns. This article intends to review these aspects in order to attain a better understanding of the implications of dietary fatty acids during perinatal development.

METABOLIC CHANGES OCCURRING IN THE MOTHER TO SUSTAIN FETAL GROWTH

Fetal metabolism, and consequently fetal growth, directly depend on the nutrients crossing the placenta, and therefore, the mother adapts her metabolism in order to support this

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continuous draining of substrates. From early gestation, the mother develops hyperphagia which together with endocrine changes, allow to increase her net body weight (free of the conceptus), corresponding mainly to the accumulation of fat depots in the first two-thirds of gestation, both in women (Hytten and Leitch, 1971; King et al., 1994; Villar et al., 1992) and in rats (López-Luna, Muñoz and Herrera, 1986; López-Luna, Maier and Herrera, 1991; Herrera et al., 1994). This fat accumulation plays a key role in maternal metabolic adaptation, since it is maintained even under conditions of severe malnutrition, despite of the decrease of energetic cost of maternal maintenance to practically zero, as it is the case in poor countries (Prentice and Golberg, 2000). During the last trimester of gestation, maternal lipid metabolism switches to a catabolic condition, as shown by an accelerated breakdown of fat depots. An enhanced adipose tissue lipolytic activity has been reported in women (Williams and Coltart, 1978; Elliott, 1975), being this change responsible for the increase in plasma free fatty acid (FFA) levels seen during the last weeks of gestation (Burt, 1960; Benassayag et al., 1997). In the rat, there is also an enhanced adipose tissue lipolytic activity during late gestation (Knopp, Herrera and Freinkel, 1970; Chaves and Herrera, 1978) which has been related to an increase in mRNA expression and activity of the hormone sensitive lipase (Martin-Hidalgo et al., 1994), the key enzyme for the lipolytic cascade.

Although in view of the above, an intense transfer of maternal adipose tissue lypolytic products, free fatty acids (FFA) and glycerol, to the fetus would be expected, this is not the case. Studies in rats and sheep have shown that glucose is the substrate crossing the placenta in the greatest amount followed by amino acids (Lasunción et al., 1987; Aldoretta and Hay, Jr., 1994; Hay, Jr., 1994), whereas FFA cross the placenta in smaller proportion, followed even at a lower rate by the second lipolytic product, glycerol (Herrera, Bonet and Lasuncion, 1998). To explain the high body fat content in humans at birth, a differential behaviour has been proposed, indicating that during early gestation, embryonic and fetal lipids are derived from maternal FFA crossing the placenta, whereas in advanced gestation, there is a gradual shift to de novo synthesis in fetal tissue (Van Aerde, Feldman and Clandinin, 1998).

What is then the main fate of the lipolytic products of maternal adipose tissue?. The answer is in plasma of the 24 h fasted pregnant rats, where lipolytic activity is highly enhanced (Herrera et al., 1988). Figure 1 shows that, as result of such enhanced lipolytic activity, plasma FFA level is higher in fasted pregnant than in virgin rats. Besides, and probably due to the limited capability of the placenta for FFA transfer, the level of FFA found in fetal plasma is low. Plasma FFA are therefore mainly directed to the liver, as it was previously seen under conditions of hepatectomy-nephrectomy in the rat, where plasma FFA levels increased more rapidly and more intensely in pregnant than in virgin rats (Mampel, Villarroya and Herrera, 1985). Circulating FFA reaching maternal liver can be used for either esterification in the synthesis of

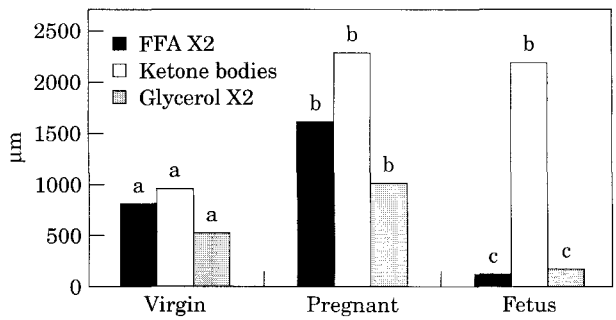

Figure 1. Plasma level of free fatty acids (FFA), ketone bodies and glycerol in 24 h fasted 20 day pregnant rats and their fetuses. Different letters indicate significant differences between groups for each variable. Methodological details as in Herrera, Gómez Coronado and Lasunción (1987).

glycerides or oxidation and ketone body synthesis. Both of these pathways are known to be enhanced in the fasted late pregnant rat (Scow, Chernick and Brinley, 1964; Herrera, Knopp and Freinkel, 1969; Zorzano and Herrera, 1988), and consequently, plasma ketone bodies level increase to values that are much higher than in virgin rats (Figure 1). Despite that ketogenesis is not active in the fetus (Scow, Chernick and Smith, 1958; Shambaugh, 1985), ketone bodies in fetal plasma reach the same level as in the mother (Figure 1) since they easily cross the placenta. The fetus therefore, benefits from this product of maternal fatty acid metabolism, since ketone bodies may be used not only as fuels (Shambaugh, 1985) but also as lipogenic substrates (Edmond, 1974; Patel et al., 1975).

As commented above, placental transfer of glycerol is also very limited, and together with the active adipose tissue lipolytic activity during late gestation, justifies the increase in plasma glycerol level seen in the 24 h fasted 20 day pregnant rat, as well as its low concentration in fetal plasma (Figure 1). Maternal glycerol is however being used as a preferential substrate for glucose synthesis in the late pregnant rat (Zorzano, Lasuncion and Herrera, 1986; Zorzano and Herrera, 1986; Herrera et al., 1992). This mechanism not only warrants the availability of glucose for placental transfer, but also saves the use of other gluconeogenic substrates like amino acids, which, as shown in women, are less available in maternal circulation (Cetin et al., 1996; Metzger, Unger and Freinkel, 1977) but are essential for fetal growth.

Lipolytic products reaching the liver can be also used for triglyceride synthesis and released into the circulation as VLDLs. This pathway is also enhanced during late pregnancy, as directly shown by the enhanced liver production of VLDL-triglycerides in the rat (Wasfi, Weinstein and Heimberg, 1980), and by the increase in plasma VLDL-triglycerides levels seen in pregnant women, which disappears after parturition (Alvarez et al., 1996). This enhanced liver production of VLDL occurs in the presence of: (i) an increase in the transfer of triglycerides among the different lipoprotein fractions, due to an increase in the cholesterol ester transfer protein (Iglesias et al., 1994), (ii) an increase in the intestinal absorption of dietary lipids (Argiles and Herrera, 1989), (iii) a reduced clearance of triglyceride-rich lipoproteins due to decreased

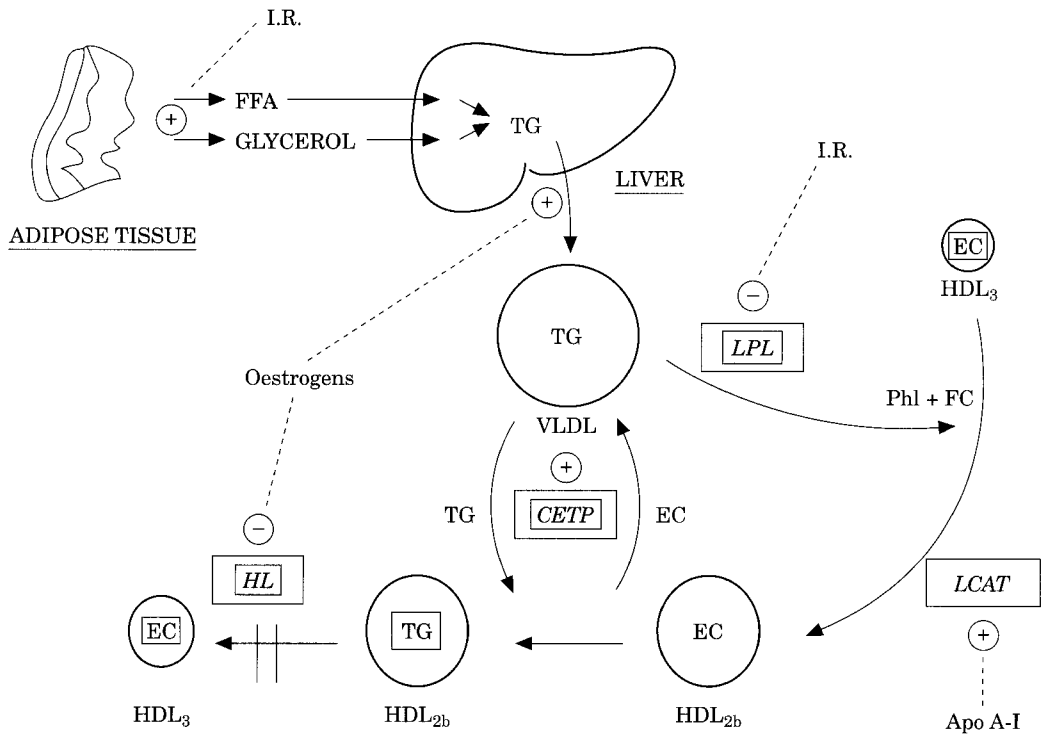

Figure 2. Schematic representation of major interactions of lipoprotein metabolism during late pregnancy. Activated steps (+) and inhibited steps (−); I.R., insulin resistance; Phl, phospholipids; FC, free cholesterol; EC, esterified cholesterol; TG, triglycerides; LPL, lipoprotein lipase; HL, hepatic lipase; CETP, cholesteryl ester transfer protein; LCAT, lecithin cholesterol acyltransferase. Adapted from Alvarez et al. (1996), with permission.

extrahepatic lipoprotein lipase (LPL) activity (Alvarez et al., 1996; Martin-Hidalgo et al., 1994), and iv) a decrease in hepatic lipase activity (Alvarez et al., 1996). In late pregnant women these changes leads to an increase in the content of triglycerides not only in VLDL but also in those lipoproteins that normally transport them in very small proportion, LDL and HDL (Alvarez et al., 1996; Montelongo et al., 1992). The accumulation of triglycerides in HDL alters the plasma profile of its subfractions in pregnant women, with a specific increment in the large triglyceride-enriched HDL_{2b} particles, and a decrease in the smaller HDL_{3a} and HDL_{3b} particles (Alvarez et al., 1996). It is proposed that all these changes are conducted by two factors, the insulin resistant condition developed during the last trimester of pregnancy (Freinkel, 1980; Catalano et al., 1993; Cousins, 1991), and the increase in circulating estrogens (Knopp et al., 1992a; Montelongo et al., 1992). In fact, the reversion of maternal insulin resistance in the late pregnant rat, has shown that insulin resistance is responsible for both the enhanced adipose tissue lipolytic activity (Ramos and Herrera, 1995) and the decrease in adipose tissue lipoprotein lipase activity (Martín, Ramos and Herrera, 1993; Herrera, Ramos and Martín, 1990). In women, the enhanced liver production of VLDL during late pregnancy has been attributed to estrogens (Knopp et al., 1992a), and although no studies have been carried out in pregnant women to determine the responsible factor for their decreased hepatic lipase activity, a therapeutic increment in estrogens in postmenopausal women has been associated to declines in hepatic lipase activity (Julius et al., 1994; Brinton, 1996). Figure 2 summarizes schematically major interactions taking place in lipoprotein metabolism during late pregnancy. The insulin-resistant condition that normally takes place at this stage of pregnancy seems to be responsible for both the decline in adipose tissue LPL activity and the enhanced adipose tissue lipolytic activity. The later change provokes an enhancement in the arrival of FFA and glycerol to the liver, increasing the availability of substrates for liver triglyceride synthesis. In this condition, estrogens exert their stimulatory effects on the release of VLDL-triglycerides, which together with their action in decreasing hepatic lipase activity, seem to actively contribute no only to the circulating increase in VLDL but to the accumulation of triglycerides in those lipoproteins of higher density than VLDL during late pregnancy (Alvarez et al., 1996; Montelongo et al., 1992).

Maternal triglycerides do not directly cross the placenta (Herrera, Bonet and Lasuncion, 1998). Besides being a source of essential fatty acids for the fetus (see below), they may be used as a source of oxidative substrates, although in an indirect manner and under a metabolic emergency condition, such as starvation. Despite that the adult liver lacks LPL expression, 24 hour starvation causes a marked increase in liver LPL activity in pregnant rats, although not in the nonpregnant rats (Testar, Llobera and Herrera, 1985; Vilaró et al., 1990), and such change is paralleled by a similar increase in liver triglycerides and plasma ketone body concentrations (Herrera et al., 1988). Such LPL activity in the liver of the starved pregnant rat seems to have an extrahepatic origin, and serves a certain purpose. Through this mechanism, the liver, a triglyceride-exporter organ under normal conditions, becomes an enhanced

acceptor of circulating triglycerides, thus allowing increased consumption of triglycerides as ketogenic substrates, and therefore contributing to the enhanced maternal ketonemia under fasting conditions. This situation not only provides ketone bodies availability to the fetus, but their use by maternal tissues must contribute to a reduced utilization of other substrates, like glucose and amino acids, which are preserved for their placental transfer to the fetus, where they are essential.

AVAILABILITY OF ESSENTIAL FATTY ACIDS TO THE FETUS

All eucaryotic organisms contain polyenoic fatty acyl chains in the complex lipids of their membranes, and although most mammalian tissues can modify acyl chain composition by introducing more than one double bond, specific limitations exist (Cook, 1991):

(a) The first double bond introduced into a saturated acyl chain is generally in the Δ9 position.
(b) Whereas plants and insects can introduce double bonds beyond the Δ9 position, this cannot be done by higher animals. Consequently, in animals double bonds are inserted only at the Δ9, Δ6, Δ5 and Δ4 positions, since well-established evidence confirms their respective desaturases in a variety of tissues.
(c) The reaction catalyzed by these desaturases requires oxygen and either NADH or NADPH, and they consist of three component proteins, NADH-cytochrome b_5 reductase, cytochrome b_5, and a cyanide-sensitive desaturase containing nonheme iron. Throughout these systems, cis double bonds are always introduced.
(d) Given the limitations of mammalian desaturases, chain elongation usually alternates with desaturation to maintain methylene interruption in polyunsaturated fatty acyl chains.

Thus, throughout the combination of desaturation and chain elongation humans may convert linoleic acid (18 : 2, ω-6) to arachidonic acid (20 : 4, ω-6) or a-linolenic acid (18 : 3, ω-3) to eicosapentaenoic acid (20 : 5, ω-3) and docosahexaenoic acid (22 : 6, ω-3), and this is the reason why linoleic (18 : 2, ω-6) and α-linolenic (18 : 3, ω-3) are the only fatty acids known to be essential for the complete nutrition, and must be supplied in the diet.

All of the ω-6 and ω-3 fatty acid structure acquired by the fetus must therefore come from the mother, crossing the placenta, either in the form of those two essential fatty acids, or their long-chain polyunsaturated fatty acid (LCPUFA) derivatives, of which, arachidonic acid (20 : 4, ω-6) and docosahexaenoic acid (22 : 6, ω-3) are metabolically the most important. Intrauterine requirements for ω-6 and ω-3 fatty acids in the human fetus during the last trimester of fetal development through the early weeks of life have been estimated to be 400 mg/kg/day and 50 mg/kg/day, respectively (Clandinin et al., 1981; Van Aerde, Feldman and Clandinin, 1998). In tissues such as the brain, where lipids constitute around 50 per cent dry weight, almost half of the total lipid content is composed of LCPUFA (Gurr, 1993). Both arachidonic acid and docosahexaenoic acid are readily incorporated into the structural lipids of the developing brain (Crawford et al., 1976), where besides their role in maintaining fluidity, permeability and conformation of the membranes, they play an important functional role. Once released from phospholipids by the action of phospholipase A_2, arachidonic acid is the main precursor for eicosanoids, prostaglandins and leukotriens, (Sellmayer and Koletzko, 1999) and is essential for neonatal growth (Carlson et al., 1992), whereas docosahexaenoic acid has been given a key role in the brain development and visual function (Birch et al., 1993; Carlson, Werkman and Pepples, 1993; Innis et al., 1996). Although the relative rates of desaturation by rat liver and brain differ between those of adult and 10 day old animals (Cook, 1991), the degree to which the human fetus is capable of desaturation and elongation is not clear. It is normally believed that the supply of essential fatty acids and LCPUFA is critical and central to the synthesis of structural lipids and, hence, to normal fetal development (Clandinin et al., 1980; Leaf et al., 1996; Hornstra et al., 1995).

Δ5- and Δ6-desaturase activities are not detectable in human placenta (Chambaz et al., 1985; Kuhn and Crawford, 1986). This is consistent with the inability of the placenta to convert γ-linolenic acid (18 : 3, ω-6) into arachidonic acid (20 : 4, ω-6) (Booth et al., 1981). Thus, the ability of the placenta to extract LCPUFA from maternal circulation and deliver them to the fetus becomes highly important. In fact, numerous studies have shown that the percentage of LCPUFA is even higher in human fetal or neonatal than in maternal circulation (Innis, 1991; Hornstra et al., 1995; Coleman, 1989; Crawford et al., 1989), although the underlying biochemical mechanisms controlling this phenomenon are not completely understood. Plasma free fatty acids (FFA), which increase rapidly during the last trimester of pregnancy (Burt, 1960; Benassayag et al., 1997), have been proposed as the main class of naturally occurring lipids transferred across the placenta, irrespective of species or the source from which they originate in the maternal circulation (Innis, 1991; Crawford, Hassan and Stevens, 1981; Stephenson, Stammers and Hull, 1993). However, as shown in Figure 3, when the amount of PUFA in the different lipid fractions in plasma of pregnant women at the 3rd trimester of pregnancy and postpartum is estimated, they are mainly esterified and associated to circulating lipoproteins rather than in the form of FFA, which practically represent a negligible amount. In fact, if the change of PUFA content in the different lipoprotein fractions between the 3rd trimester and postpartum is considered, it appears that those present in triglycerides of VLDL, LDL and HDL are the lipidic moieties that show the greater decline at postpartum, whereas the chain found in phospholipids or esterified cholesterol are milder, and even absent as is the case of HDLs. In fact, the greatest effect produced by pregnancy as compared to postpartum, on circulating PUFA concentrations is found in those present in both

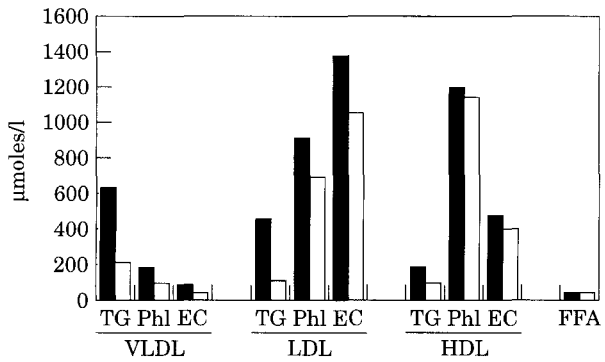

Figure 3. Concentration of PUFA in plasma lipidic fractions of lipoproteins and FFA in women during the 3rd trimester of pregnancy and postpartum. TG, triglycerides; Phl, phospholipids; EC, esterified cholesterol. Lipoproteins were isolated by sequential ultracentrifugation and PUFA quantified as previously described (Montelongo et al., 1992; Arranz, 1993). Solid bars: third trimester; open bars: post partum.

VLDL- and LDL-triglycerides, whereas those present in FFA did not show any significant change (Figure 3).

Thus, in spite of the lack of a direct placental transfer of triglycerides (Herrera, Bonet and Lasuncion, 1998; Shand and Noble, 1979), essential fatty acids derived from maternal diet, which are transported as triglycerides in triglyceride-rich lipoproteins in maternal plasma, have to become available to the fetus. This occurs thanks to the presence of lipoprotein receptors in the placental trophoblast cells, located at the interface with maternal blood, that function both as endothelium and transporting epithelium. Hence, trophoblast cells are positioned to bind maternal lipoproteins and mediate their metabolism and subsequent transfer of the PUFA they deliver to the fetal circulation. Human placental tissue has been shown to express very low density lipoprotein/apo E receptor (VLDLR) as well as LDL receptor (LDLR) and LDL receptor-related protein (Cummings et al., 1982; Winkel, MacDonald and Simpson, 1981; Winkel et al., 1980; Gafvels et al., 1993; Albrecht et al., 1995; Overbergh et al., 1995; Alsat et al., 1982, 1984; Malassine et al., 1987). It has been shown even that maximal capacity of VLDL binding was 4.5 greater than that of LDL, and that the relative abundance ratio of VLDLR/LDLR mRNA is greatest at term (Wittmaack et al., 1995). Although the presence of a putative HDL receptor (that binds apo A-I) in placental membrane preparations (Graham and Oram, 1987) that could be implicated in the efflux rather than the influx of cholesterol to the cells (Brinton et al., 1985; Schmitz et al., 1985) was also reported, it was also shown that HDL_2 cholesterol is taken up by trophoblast cells through a receptor-independent mechanism, which may contribute to the supply of cholesterol to the placenta for progesterone synthesis (Lasuncion, Bonet and Knopp, 1991). Specific HDL_3 binding without internalization has been demonstrated in human placental microvilli (Alsat and Malassine, 1991).

Placental tissue from different species has been shown to express lipoprotein lipase (LPL) activity (Elphick and Hull, 1977; Rotherwell and Elphick, 1982; Bonet et al., 1992) as well as phospholipase A_2 (Farrugia et al., 1993; Rice et al., 1998) and intracellular lipase activities (Biale, 1985; Kaminsky et al., 1991; Mochizuki et al., 1975). Through this mechanism, maternal plasma triglycerides are hydrolyzed and taken up by the placenta, where reesterification and intracellular hydrolysis facilitates diffusion of the released fatty acids to the fetus, and their subsequent transport to fetal liver. In fact, the use of cultured placental trophoblast cells has shown that esterified cellular lipids provide a reservoir of fatty acids that can be released into the medium (Coleman and Haynes, 1987). The overall picture of the placental transfer of PUFA from maternal to fetal circulation has been schematically summarized (Figure 4).

Placental released FFA at the fetal side are transported in fetal blood bound to a specific oncofetal protein, the alpha-fetoprotein (AFP) (Parmelee, Evenson and Deutsch, 1978; Benassayag et al., 1980, 1997). Those fatty acids are rapidly taken up by fetal liver, where they are esterified and released back into circulation as triglycerides. Thus, a significant linear correlation is developed for certain LCPUFA between maternal plasma and cord plasma triglycerides during late gestation in human (Berghaus, Demmelmair and Koletzko, 2000). Also a linear correlation between maternal and fetal plasma triglycerides was also found in the rat, when maternal plasma triglycerides concentration are modified by a streptozotocin diabetic condition and treated with different insulin schedules (Figure 5). This correlation between maternal and fetal triglycerides may also have important implications in newborn weight, since a direct relationship has been consistently found in human between maternal plasma triglycerides and newborn weight (Kitajima et al., 2001; Skryten et al., 1976; Knopp et al., 1992b).

Although in a smaller proportion than lipoprotein triglycerides, maternal plasma FFA are also an important source of PUFA to human fetus (Kuhn and Crawford, 1986; Coleman, 1989; Benassayag et al., 1997). There is now evidence that cellular uptake of FFA occurs through facilitated membrane translocation involving a plasma membrane fatty acid-binding protein ($FABP_{pm}$) (Abumrad, Park and Park, 1984; Goresky et al., 1994). It has been shown that $FABP_{pm}$ is present both in sheep (Campbell, Gordon and Dutta-Roy, 1996) and human placental membranes (Campbell, Gordon and Dutta-Roy, 2000), being also responsible for the preferential uptake of LCPUFA by the human placenta (Campbell, Gordon and Dutta-Roy, 1996; Campbell et al., 1997). The preference for human placental transfer from the maternal to the fetal circulation has been reported to be docosahexaenoic>α-linolenic>linoleic>oleic>arachidonic acid (Haggarty et al., 1997). Arachidonic acid was however the fatty acid showing the highest accumulation by the placenta (Haggarty et al., 1997), and a recent study has shown that arachidonic acid uptake by placental syncytiotrophoblast membranes is highly dependent on ATP and sodium (Lafond et al., 2000) implying an active transport mechanism for this fatty acid. A selectivity in the LCPUFA placental transfer may also be exerted at the level of cellular metabolism, as evidenced by other authors, reporting that a certain proportion of arachidonic acid is

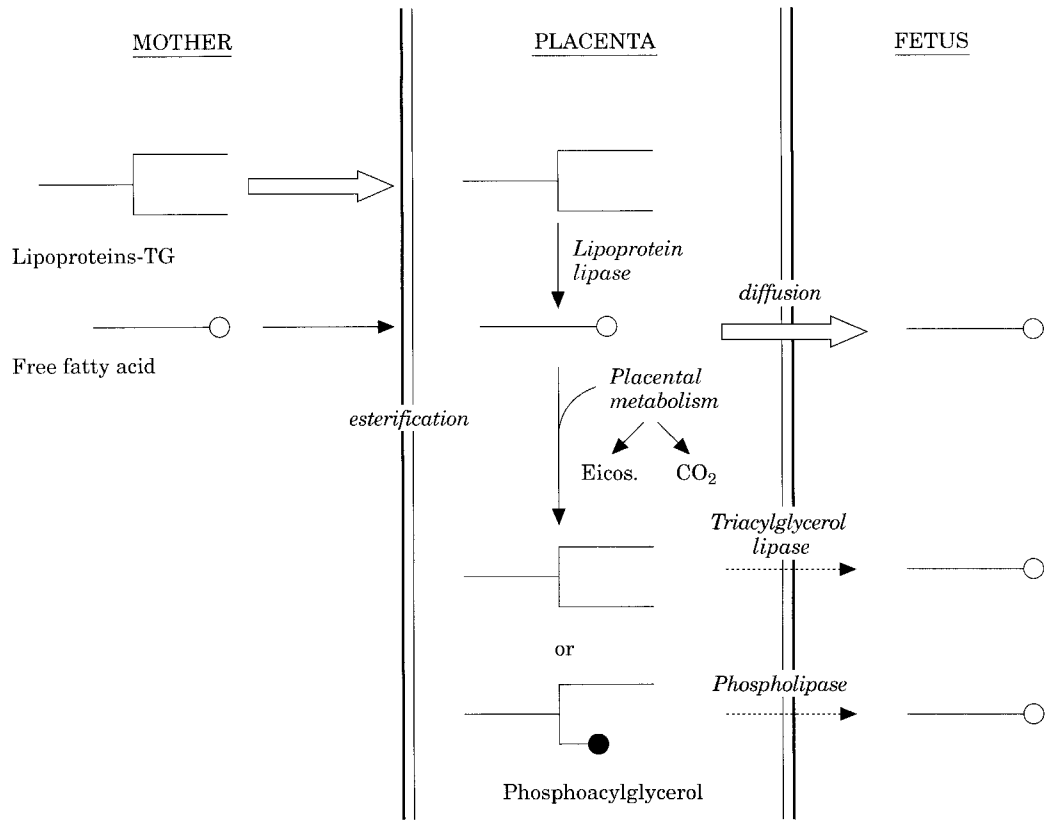

Figure 4. Schematic representation of the placental transfer of fatty acids to the fetus.

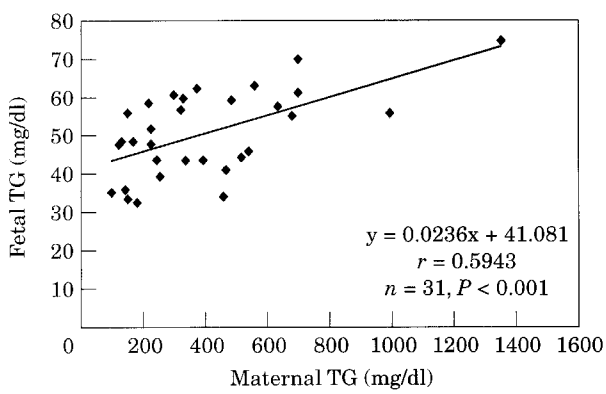

Figure 5. Linear correlation between maternal and fetal plasma triglycerides in 20 d pregnant rats having different degrees of diabetes in order of attaining different plasma levels of triaglycerides. Rats were treated only once with 45 mg streptozotocin i.v./kg body weight before mating and supplemented with s.c. insulin (1.5 IU/day per 100 body weight) for different periods of time during pregnancy in order of developing different degrees of diabetes, as previously described (Martín and Herrera, 1991).

converted to prostaglandins (Kuhn and Crawford, 1986). Also, a selective incorporation of certain fatty acids into phospholipids has been found in the ovine placenta (Shand and Noble, 1985), and even a selective placental fatty acid oxidation (Zimmermann et al., 1979; Robertson, Sprecher and Karp, 1971) and lipid synthesis (Tulenko and Rabinowitz, 1981; Coleman and Haynes, 1987; Robertson and Sprecher, 1967) have been reported.

The combination of all those processes determines the actual rate of placental fatty acids transfer and its selectivity. Through these mechanisms, the placenta selectively transports arachidonic acid and docosahexaenoic acid from the maternal to the fetal compartment, resulting in an enrichment of these LCPUFAs in circulating lipids in the fetus (Crawford et al., 1976). This occurs during the third trimester, when fetal demand for neural and vascular growth are greater (Innis, 1991; Simopoulos, 1991; Uauy et al., 2000).

IMPLICATIONS OF DIETARY FATTY ACIDS DURING PREGNANCY AND LACTATION IN THE OFFSPRING

The supply of essential fatty acids and LCPUFA is critical and central to the synthesis of structural lipids and hence, to normal development of the fetus (Clandinin et al., 1980; Foreman-van Drongelen et al., 1995; Leaf et al., 1992a; Neuringer and Connor, 1986). Although formation of arachidonic acid and docosahexaenoic acid from parent essential fatty acid precursors has been shown in term and preterm infants (Sauerwald et al., 1997; Demmelmair et al., 1995; Salem, Jr. et al., 1996; Carnielli et al., 1996; Uauy et al., 2000), the degree to which the fetus is capable of fatty acid desaturation and elongation is not clear. Fetal baboons have been shown to effectively synthesize both docosahexaenoic acid (22 : 6, ω-3) and arachidonic acid (20 : 4, ω-6) from their precursors,

α-linolenic acid (18 : 3, ω-3) and linoleic acid (18 : 2, ω-6) respectively (Su et al., 1999, 2001). However, the small contribution of endogenous synthesis of arachidonic acid to the plasma arachidonic acid pool in newborn infants during the first week of life has been demonstrated (Szitanyi et al., 1999). A low enzymatic activity of Δ-5-desaturation has been proposed as one factor limiting arachidonic acid synthesis (Demmelmair et al., 1998), and although high Δ5- and Δ6-desaturase activities in the liver of one 18 week and two 22 week fetuses (Chambaz et al., 1985), which were close to those found in adult liver (De Gómez Dumm and Brenner, 1975) have been reported, human fetal liver desaturase-elongase chain reaction has not been clearly demonstrated in physiological conditions.

The nutritional status of the mother during gestation has been related to fetal growth, and, in general, reduced nutritional status with respect to ω-6 and ω-3 essential fatty acids has been correlated with reduced neonatal growth and head circumference in humans (Jumpsen, Van Aerde and Clandinin, 1997). Significant lineal correlations between the mother and fetus or newborn has been found for both LCPUFA ω-3 or ω-6 fatty acids in untreated healthy women (Crastes de Paulet et al., 1992; Al et al., 1990; Matorras et al., 1999). Parallel increases in plasma docosahexaenoic acid in the mothers and newborns were also found after fish-oil supplementation during pregnancy (Van Houwelingen et al., 1995; Connor, Lowensohn and Hatcher, 1996). These show the importance of maternal dietary fatty acids controlling the availability of LCPUFA to the fetus and newborn. In fact, since it is considered that the developing fetus depends mainly, or completely, on the maternal supply for essential fatty acids, the supplement with LCPUFA-rich oils during the last trimester of pregnancy to increase levels in neonates, has been advised (Van Houwelingen et al., 1995; Connor, Lowensohn and Hatcher, 1996). However, the competitive desaturation of the ω-3 and ω-6 series by Δ6- and Δ5-desaturases is of major significance because of their controlling role in the desaturating and elongating pathways of the parent essential fatty acids (Uauy-Dagach and Mena, 1995). Thus, whereas excessive dietary intake of linoleic acid from vegetable oils may inhibit Δ6-desaturase, particularly safflower, sunflower, and corn oils, that would result in a decrease in the formation of docosahexaenoic acid from α-linolenic acid, arachidonic acid formation is lower when excessive linoleic acid is provided, as seen in enterally or parenterally fed infants receiving corn or safflower oil as the predominant source of fatty acids (Brenner and Peluffo, 1969; Innis, 1991; Simopoulos, 1991; Sprecher, 2000). Besides, the inhibitory effect of eicosapentaenoic acid on Δ5-desaturase activity has been considered responsible for the lower plasma arachidonic acid found when fish oil, high in eicosapentanoic acid and docosahexaenoic acid, is consumed (Uauy-Dagach and Mena, 1995). Also, inhibition of Δ6 desaturase activity by fish oil has been demonstrated, being also responsible for major declines in arachidonic acid levels (Garg, Thomson and Clandinin, 1990; Raz et al., 1997). The consumption of fish oils modifies membrane phospholipid composition, increasing eicosapentaenoic and docosahecaenoic acids concentrations at the expense of arachidonic acid content, and adverse effects of low arachidonic acid concentration in serum and red blood cell phospholipids on growth during infancy have been reported (Koletzko and Braun, 1991; Carlson et al., 1991; Carlson, Werkman and Pepples, 1993). In fact, at birth, arachidonic acid status in preterm infants has been correlated with their body weight (Koletzko and Braun, 1991; Leaf et al., 1992b), and it has been proposed that it is related rather to intra-uterine growth than to post-natal growth (Woltil et al., 1998).

Foods containing lipid peroxides are potentially toxic, and the higher content in PUFAs in the diet, the more likely will peroxidation occur (Halliwell and Chirico, 1993; Esterbauer, 1993; Berry et al., 1991). Thus, excess intake of PUFA may reduce antioxidant capacity (Cho and Choi, 1994), enhancing susceptibility to oxidative damage (Mazière et al., 1998), a condition that has been shown to be responsible for fetal damage during pregnancy in rats (Viana, Herrera and Bonet, 1996; Simán and Eriksson, 1997; Viana et al., 2000). Thus, the potential negative effect of high dietary fish oil intake on offspring during pregnancy could be modulated not only by decreased arachidonic acid concentrations but also by decreased vitamin E concentrations.

Different to fish oil, dietary olive oil protects the ω-3 PUFA series (Navarro et al., 1994), does not affect arachidonic acid concentrations (Girón et al., 1989; Periago, Suarez and Pita, 1990; Rao, Zang and Reddy, 1993) and is much more resistant to lipid peroxidation (Scaccini et al., 1992; Oztezcan, Toker and Uysal, 1996; Berry et al., 1991). Thus, the effect of a diet supplemented with 10 per cent fish oil as the only nonvitamin lipid component versus the same amount of olive oil during pregnancy on the fatty acid profile and vitamin E concentration was studied in the rat. A decrease in both arachidonic acid and α-tocopherol concentrations as well as a delayed postnatal development was found in the offspring of rats fed the fish oil-rich diet (Amusquivar et al., 2000). The study was extended to determine whether dietary supplementation with either vitamin E or γ-linolenic acid (18 : 3, ω-6), as a precursor of arachidonic acid, could ameliorate these changes. Whereas arachidonic acid concentrations and postnatal development indexes, although not α-tocopherol concentrations, were recovered when the fish-oil diet was supplemented with γ-linolenic acid, postnatal development indexes were not recovered when the fish oil-rich diet was supplemented with sufficient exogenous vitamin E to normalize α-tocopherol levels (Amusquivar et al., 2000). Thus, it was concluded that although feeding a fish oil-rich diet during pregnancy and lactation decreased both α-tocopherol and arachidonic acid concentrations, the latter deficiency rather than the former seemed to be responsible for delayed postnatal development of rat pups. In this same study, another group of pregnant and lactating rats fed the fish oil-rich diet received a supplement with arachidonic acid instead of γ-linolenic acid, and although both treatments restored brain phospholipid arachidonic acid content in pups, the effect restoring delayed growth rate and

neurodevelopment indexes was more efficient in the latter than in the former group. The only difference between them was the absence of linoleic acid (18 : 2, ω-6) in brain phospholipids when rats were supplemented with arachidonic acid, whereas it was present at a normal level in those supplemented with γ-linolenic acid (Amusquivar et al., 2000). These findings agree with those previously found in humans fed diets rich in arachidonic acid, in which the proportion of linoleic acid in plasma phospholipids decreased (Sinclair and Mann, 1996), the effect being likely a consequence of replacing linoleic acid by arachidonic acid in tissues (Whelan, 1996). It is therefore worth emphasizing the exquisite sensitivity of endogenous LCPUFA metabolism to changes in maternal dietary fatty acid composition during perinatal development, and its consequences to postnatal development.

Since benefits and risks of modifying maternal fat intake in pregnancy and lactation are not yet completely established, and the safety of high intakes of LCPUFA during pregnancy is still unclear (Brown and Kahn, 1997; Hamosh, 1998; Eritsland, 2000; Lauritzen et al., 2001), confirmation of results is required before recommendations to increase LCPUFA intake in pregnancy can be made.

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