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Lipid Metabolism in Pregnancy and its Consequences in the Fetus and Newborn

Emilio Herrera

Facultad de Ciencias Experimentales y de la Salud, Universidad San Pablo-CEU, Madrid, Spain

During early pregnancy there is an increase in body fat accumulation, associated with both hyperphagia and increased lipogenesis. During late pregnancy there is an accelerated breakdown of fat depots, which plays a key role in fetal development. Besides using placental transferred fatty acids, the fetus benefits from two other products: glycerol and ketone bodies. Although glycerol crosses the placenta in small proportions, it is a preferential substrate for maternal gluconeogenesis, and maternal glucose is quantitatively the main substrate crossing the placenta. Enhanced ketogenesis under fasting conditions and the easy transfer of ketones to the fetus allow maternal ketone bodies to reach the fetus, where they can be used as fuels for oxidative metabolism as well as lipogenic substrates. Although maternal cholesterol is an important source of cholesterol for the fetus during early gestation, its importance becomes minimal during late pregnancy, owing to the high capacity of fetal tissues to synthesize cholesterol. Maternal hypertriglyceridemia is a characteristic feature during pregnancy and corresponds to an accumulation of triglycerides not only in very low-density lipoprotein but also in low- and high-density lipoprotein. Although triglycerides do not cross the placental barrier, the presence of lipoprotein receptors in the placenta, together with lipoprotein lipase, phospholipase A_2, and intracellular lipase activities, allows the release to the fetus of polyunsaturated fatty acids transported as triglycerides in maternal plasma lipoproteins. Normal fetal development needs the availability of both essential fatty acids and long chain polyunsaturated fatty acids, and the nutritional status of the mother during gestation has been related to fetal growth. However, excessive intake of certain long chain fatty acids may cause both declines in arachidonic acid and enhanced lipid peroxidation, reducing antioxidant capacity.

Key Words: Lipid metabolism; pregnancy; placenta; fatty acids; cholesterol; triglycerides.

Introduction

Fetal development is sustained by the metabolites crossing the placenta at the expense of those present in maternal circulation. Glucose is quantitatively the most important nutrient crossing the placenta, followed by amino acids *(1–5)*, and the development of the fetus directly depends on their continuous availability. However, although the placental transfer of lipid components is very limited *(6)*, they also play a major role in fetal development. Changes in the availability of lipid components, like those produced by changes in dietary fatty acids, are known to have implications in fetal and postnatal development *(7)*. In addition, adaptations of maternal lipid metabolism taking place throughout gestation also have major consequences for fetal growth. It is known that deviations in maternal hyperlipidemia, such as those caused by hypercholesterolemia, even when temporary and limited to pregnancy, trigger pathogenic events in the fetal aorta and may lead to atherosclerosis later in life *(8–10)*. Two consistent manifestations of altered maternal lipid metabolism normally occurring during gestation are the accumulation of lipids in maternal tissues *(11,12)* and the development of maternal hyperlipidemia *(13,14)*. Conditions known to alter any of these manifestations by impairing maternal fat depot accumulation, such as hypothyroidism or overt diabetes during the first half of gestation, greatly affect fetal growth at late gestation, even if they are compensated for by appropriate hormonal treatment during the second half of gestation *(15,16)*. These findings therefore emphasize the important role of maternal lipid metabolism on fetal growth and late pregnancy outcome, despite the difficulties of lipids crossing the placenta. This article reviews the changes that occur in maternal lipid metabolism during gestation and how they contribute to fetal and postnatal development.

Adipose Tissue Metabolism: Lipolytic Activity

An accelerated breakdown of fat depots occurs in both women and rats during the last third of gestation *(17–21)*, and higher activity and mRNA expression of the key enzyme for adipose tissue lipolysis, hormone-sensitive lipase, in late pregnant rats have been reported *(22)*. As will be discussed, despite the enhanced release of lipolytic products, nonesterified fatty acids (NEFA) and glycerol into maternal circulation, their placental transfer is quantitatively low *(6)*. The

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Author to whom all correspondence and reprint requests should be addressed: Dr. Emilio Herrera, Universidad San Pablo-CEU, Ctra. Boadilla del Monte km 5,300, E-28668 Boadilla del Monte, Madrid, Spain. E-mail: eherrera@ceu.es

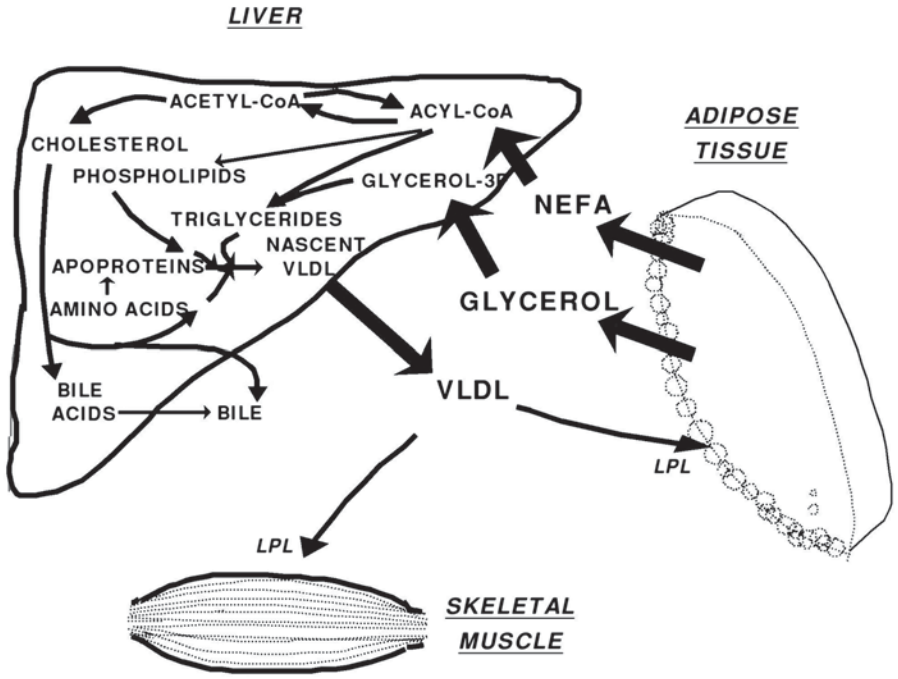

Fig. 1. Schematic representation of utilization by the liver of adipose tissue lipolytic products, NEFA and glycerol, as substrates for triglyceride synthesis and VLDL production for their catabolism by extrahepatic tissues. LPL = Lipoprotein lipase.

main destiny of these products is the liver *(23)*, where, after the conversion of NEFA into acyl-CoA and glycerol into glycerol-3-phosphate, they are reesterified for the synthesis of triglycerides (Fig. 1). These are incorporated into nascent very low-density lipoprotein (VLDL) particles, which are then released into the circulation, where they are converted into mature VLDLs. Since insulin may inhibit VLDL secretion *(24)*, a maternal insulin-resistant condition may contribute to the increased VLDL production. However, augmented estrogen concentration at late pregnancy seems to be the major activator of VLDL liver production *(14)*.

Under fasting conditions during late pregnancy, maternal adipose tissue lipolytic activity becomes highly enhanced *(20,21,25,26)*. A heightened catecholamine excretion *(27, 28)* secondary to maternal hypoglycemia even under mild dietary deprivation, together with the increased amount of gestational hormones released by the placenta and ovary, as well as the insulin-resistant condition, seems to be responsible for higher lipolytic activity of maternal adipose tissue.

Maternal plasma concentration of glycerol and NEFA increase during late gestation *(21,26,29)* as a consequence of the enhanced adipose tissue lipolytic activity. Besides the use of those lipolytic products in the synthesis of triglycerides, glycerol may be used for glucose synthesis and NEFA for β-oxidation to acetyl-CoA and ketone body synthesis. These metabolic pathways become enhanced under fasting conditions at late pregnancy, when the use of glycerol for gluconeogenesis is even higher than other more classic gluconeogenetic substrates, such as alanine and pyruvate *(30, 31)*. Under this condition of food deprivation, ketogenesis is also greatly heightened in maternal liver *(32,33)*.

Increased gluconeogenesis from glycerol and ketogenesis from NEFA may benefit the fetus, which at late gestation is at its maximum accretion rate and its requirements for substrates and metabolic fuels are greatly augmented. The preferential use of glycerol for gluconeogenesis and the efficient placental transfer of the newly formed glucose may be of major importance to the fetus under these fasting conditions (Fig. 2), in which the availability of other essential substrates such as amino acids is reduced *(30,34)*. Placental transfer of ketone bodies is highly efficient *(35)*, reaching fetal plasma at the same level as in maternal circulation *(29)*. Ketone bodies may be used by the fetus as fuels *(36)* and as substrates for brain lipid synthesis *(37)*.

Accumulation of Body Fat

Accumulation of fat is one of the most common characteristics of pregnancy, occurring in both women *(11,12,38)* and experimental animals *(39–42)*, and accounts for most of the conceptus-free increase in maternal body weight during gestation *(12,39,43)*. The increase in maternal fat depots occurs during the first two-thirds of gestation, whereas it declines or even stops during the last third *(11,39,44,45)*, the latter corresponding to the phase of most accelerated lipolytic activity of adipose tissue.

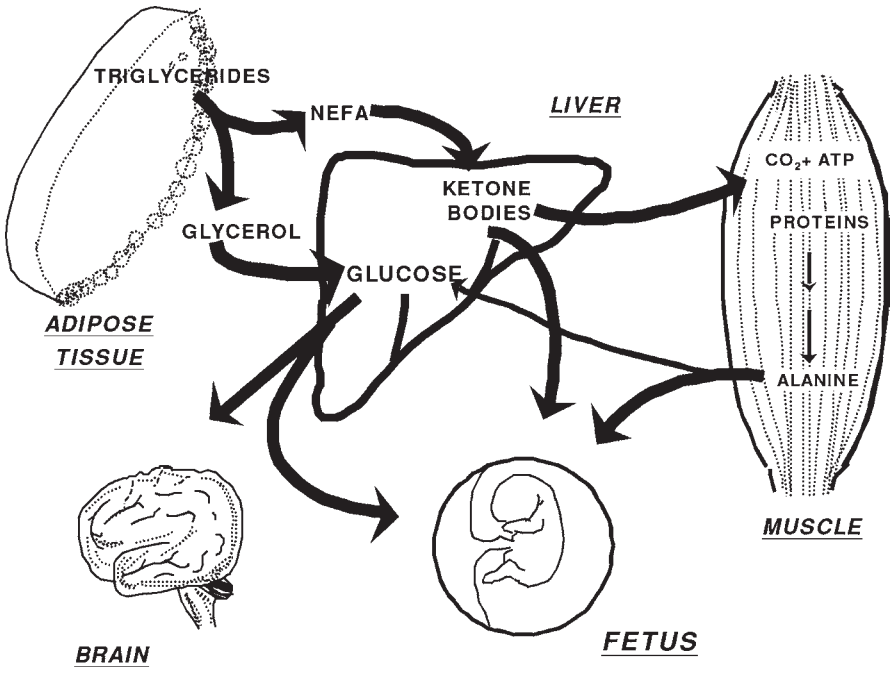

Fig. 2. Schematic representation of role of adipose tissue triglyceride stores as source of NEFA and glycerol for liver ketogenesis and gluconeogenesis during late pregnancy in fasting condition, to sustain availability of substrates for fetal and maternal tissues.

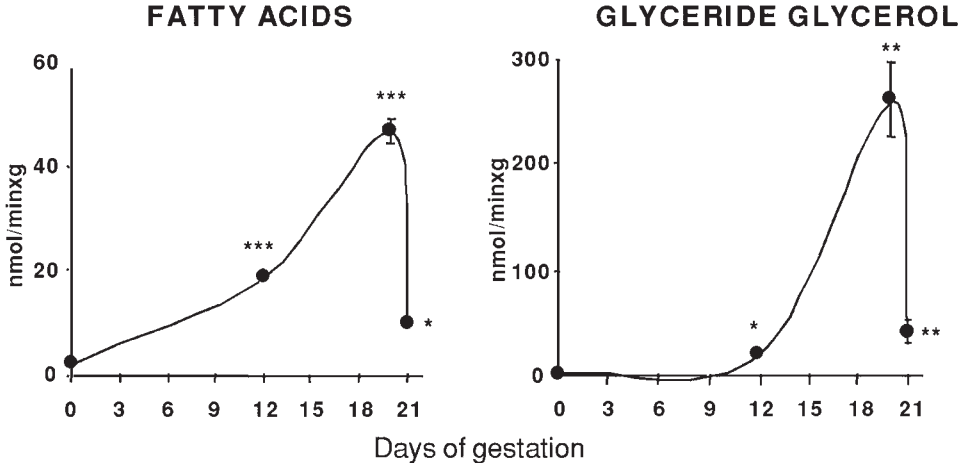

Fig. 3. Glucose utilization for fatty acid and glyceride glycerol synthesis by periuterine adipose tissue *in situ* during gestation in rat. Methodologic details are as described in ref. *51*. *Statistical comparisons vs virgin rats (0 d: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

Accumulation of body fat during early pregnancy has been associated with both hyperphagia and increased lipogenesis. Hyperphagia is present in both pregnant women *(46,47)* and rats *(41,48)*, and increases as gestational time advances. This progressive increase in the availability of exogenous substrates actively contributes to maternal accumulation of fat depots. As recently reviewed, the total energy cost of fat deposition in women from poor countries is lower than in those from well-nourished populations *(49)*, and in the rat it is not found under food-restricted conditions *(41,42,48)*.

Fatty acid and glyceride glycerol synthesis from glucose by rat periuterine adipose tissue *in situ* progressively increases until d 20 of gestation to sharply decline on d 21 *(50,51)* (Fig. 3). Enhanced fatty acid synthesis was also found in pregnant rats when studied in vivo *(52)*, and this increased lipid synthesis seems to actively contribute to the fat accumulation occurring during gestation.

A proportional increase in adipose tissue lipoprotein lipase (LPL) activity could also contribute to the fat accumulation found during early pregnancy. This enzyme is normally bound

in its active form to the capillary endothelium of extrahepatic tissues *(53)* and hydrolyzes triglycerides circulating in plasma in the form of triglyceride-rich lipoproteins, chylomicrons, and VLDLs (Fig. 1), which are respectively converted into remnant particles and intermediate-density lipoproteins. The hydrolytic products, NEFA and glycerol, are partially taken up by the subjacent tissue *(54)*, and, therefore, LPL controls the fat uptake in adipose tissue. Although a few reports have shown that at d 12 of gestation in pregnant rats there is an increase in the LPL activity of adipose tissue *(34,55)*, the change is small and not always reproduced *(22)*. No significant change has been found in the postheparin LPL activity in pregnant women at midgestation *(13)*. Thus, enhanced LPL activity of adipose tissue does not seem to contribute substantially to the accumulation of body fat taking place during the first part of gestation.

However, during late pregnancy, adipose tissue LPL consistently decreases in the rat *(44,56–58)*, and postheparin LPL also decreases in women at the third trimester of pregnancy *(13,59)*. These findings indicate that fat uptake by adipose tissue decreases during late pregnancy, which together with the enhanced lipolytic activity mentioned earlier, result in a net accelerated breakdown of fat depots. Thus, the anabolic condition of adipose tissue present during early pregnancy switches to a net catabolic condition during the last trimester of pregnancy, coinciding with the phase of maximal fetal growth. These changes contribute to the development of maternal hyperlipidemia, which besides other lipids, includes increments in plasma levels of NEFA *(60)*, sparing glucose, which is essential not only to certain maternal tissues, such as brain, but also to sustain fetal development.

Enhanced maternal insulin levels and changes in insulin sensitivity taking place throughout pregnancy may be directly or indirectly responsible for the early anabolism and late catabolism present in maternal adipose tissue in pregnancy. During early pregnancy, heightened activity of pancreatic β-cells is developed, as shown by the augmented insulinotropic effect of glucose seen in both women and rats *(61–63)*. At this stage, insulin sensitivity is either unchanged or even augmented *(64–66)*. Since both glycerolgenesis and lipogenesis from glucose are pathways sensitive to insulin, maternal hyperinsulinemia whenever the mother eats must contribute to her active deposition of fat depots. The situation changes drastically during the last third of gestation, when, despite maternal hyperinsulinemia, a major insulin-resistant condition develops *(66–70)*. The reversion of insulin resistance in the late pregnant rat *(71)*, as well as studies in isolated adipocytes from pregnant women *(18)*, has shown that insulin resistance is responsible for both enhanced adipose tissue lipolytic activity and decreased LPL activity of adipose tissue *(72)*.

The transition from an anabolic to a catabolic condition in maternal adipose tissue metabolism coincides with the maximal fetal growth phase *(44,66)*, i.e., when the mother needs to progressively increase the supply to the fetus. As discussed next, this situation causes the development of maternal hyperlipidemia, which spares glucose and other essential metabolites, such as amino acids, for the fetus, and therefore is of major importance not only to maternal metabolic economy but to fetal development.

Hyperlipidemia

Maternal hypertriglyceridemia is also a characteristic feature during late pregnancy, whereas rises in phospholipids and cholesterol are smaller *(14)*. This change corresponds not only to an increment in VLDLs but also to an enrichment of triglycerides in other lipoprotein fractions that normally do not transport them, such as low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs) *(13)*. Even within the HDL subfractions, there is a specific increment in the proportion of triglycerides in the HDL_{2b} subfraction at the expense of the HDL_{2a} or HDL_3, which are rich in cholesterol *(13)*. The greatest increase in plasma triglycerides corresponds to the VLDL triglycerides *(13, 73)*, synthesized in the liver. The main factors inducing this increase in plasma VLDL triglycerides during gestation are their enhanced production by the liver *(74,75)* and their decreased removal from the circulation as a consequence of reduced LPL activity of adipose tissue *(13,22)*.

An increase in cholesteryl ester transfer protein activity taking place at midgestation *(13,76)*, together with the abundance of VLDL triglycerides, seems to contribute to the accumulation of triglycerides in the other lipoproteins, LDL and HDL *(13,73)*, which under nonpregnant conditions are normally poor in this lipid moiety. Another factor contributing to this same effect is the decrease in the hepatic lipase activity, which also occurs during late pregnancy *(13)*. The decrease in this enzyme activity decreases the conversion of buoyant HDL_2 triglyceride-rich particles into small HDL_3 triglyceride-poor particles, allowing a proportional accumulation of the former *(13)*. These interactions taking place in lipoprotein metabolism during late pregnancy are schematically summarized in Fig. 4.

Both the insulin-resistant condition and the increase in plasma estrogen levels occurring during late pregnancy are the main hormonal factors responsible for these metabolic changes addressing to the development of maternal hypertriglyceridemia. The insulin-resistant condition constantly present during late gestation is known to contribute to both enhanced lipolytic activity of adipose tissue, which, as discussed, augments the arrival of glycerol and NEFA to the liver and their subsequent conversion into triglycerides, which are released back into the circulation in the form of VLDL *(71)*, and the decreased LPL activity *(72)*. The progressive increase in plasma estrogen levels during gestation *(77,78)* also actively contributes to maternal hypertriglyceridemia; it has been shown to enhance liver production of VLDL *(79, 80)* and decrease the expression and activity of hepatic lipase in liver *(81,82)*.

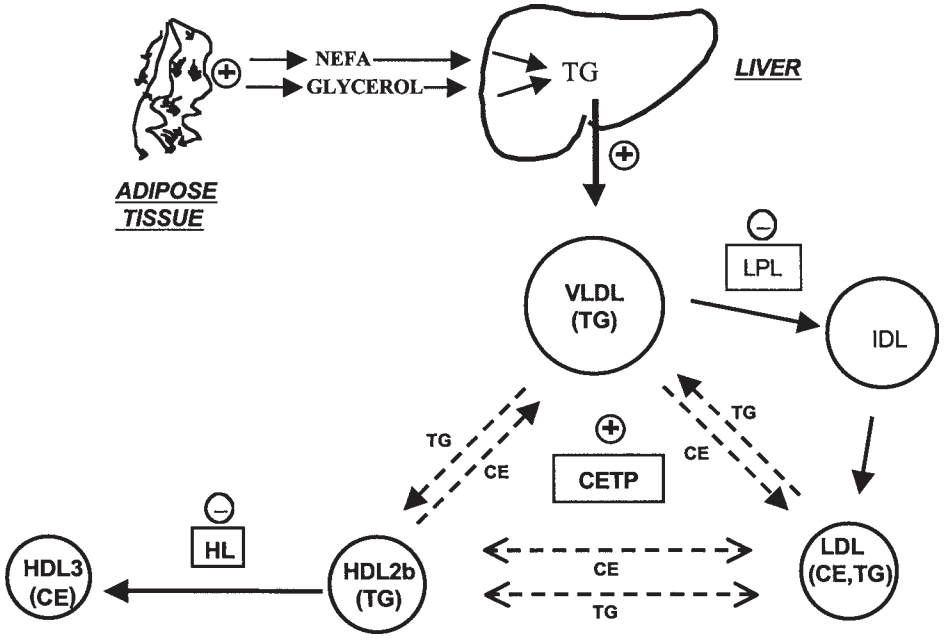

Fig. 4. Schematic representation of lipoprotein interactions during third trimester of pregnancy, causing an increase in triglyceride (TG) content of main plasma lipoprotein fractions. IDL, intermediate-density lipoproteins; CETP, cholesterol ester transfer protein; CE, cholesterol esters; HL, hepatic lipase. See text for additional explanations.

Role of Maternal Hypertriglyceridemia as a Source of Fatty Acids for the Fetus

Although triglycerides do not directly cross the placental barrier *(6)*, essential fatty acids (EFA) derived from maternal diet, which are transported as triglycerides in triglyceride-rich lipoproteins in maternal plasma *(7)*, must become available to the fetus. Placental trophoblast cells have been shown to express both very low-density/apo E receptor as well as LDL receptor–related proteins *(83–88)*. In addition, they also express LPL activity *(89–91)* as well as phospholipase A_2 *(92,93)* and intracellular lipase activities *(94–96)*.

Maternal triglycerides in plasma lipoproteins are therefore hydrolyzed and taken up by the placenta, where they are reesterified to provide a reservoir of fatty acids *(97)*. After the intracellular hydrolysis of glycerides releases fatty acids diffusely to fetal plasma, they bind to a specific oncofetal protein, the α-fetoprotein *(98,99)*. Fatty acids are then rapidly transported to fetal liver, where they are reesterified and released back into circulation in the form of triglycerides.

Because the amount of polyunsaturated fatty acids present in plasma in the form of NEFA represents a minor proportion as compared to those carried in the form of lipoproteins *(7)* (Fig. 5), the mechanism described indicates that maternal hyperlipoproteinemia plays a key role in the availability of EFA to the fetus. In fact, a linear correlation has been found between maternal and fetal plasma triglycerides in the rat *(7,100)*, and a direct relationship between maternal triglycerides and newborn weight has been found in humans *(101–103)*. Furthermore, a reduction in maternal hypertriglyceridemia, such as that caused by treatments with hypolipidemic drugs, has negative effects in fetal development *(104,105)*.

Transfer of Lipid Metabolites to the Fetus

Nonesterified Fatty Acids

The net flux of fatty acids crossing the placenta differs among species. In species with a placenta having both maternal and fetal layers, such as sheep, pig, and cat, the maternal fetal fatty acid transfer is small *(106–109)*. In species in which the placenta is formed by layers of fetal origin, such as rabbit *(110)*, guinea pig *(111)*, primate *(112)*, and rat *(113,114)*, the amount of fatty acids crossing the placenta exceeds even that needed to fulfill lipid storage requirements *(115)*. In humans, although in a smaller proportion than lipoprotein triglycerides (Fig. 5), maternal plasma NEFA are an important source of polyunsaturated fatty acids for the fetus *(116,117)*.

The plasma membrane fatty acid–binding protein present in human placental membranes *(118,119)* is responsible for the preferential uptake of long chain polyunsaturated fatty acids (LCPUFA). Besides the preference for human placental transfer for certain fatty acids—docosahexaenoic (DHA) > α-linolenic > linoleic > oleic > arachidonic acid (AA) *(120)*—the uptake of arachidonic acid by syncytiotrophoblast membranes has been shown to occur via an active process, highly dependent on ATP and sodium *(121)*. A selective cellular metabolism of certain fatty acids may

also contribute to the placental transfer process, as would the conversion of a certain proportion of arachidonic acid to prostaglandins *(117)*, the incorporation of some fatty acids into phospholipids *(122)*, the oxidation of placental fatty acids *(123)*, and the synthesis of fatty acid *(124)*.

The combination of all these processes determines the actual rate of placental fatty acid transfer and its selectivity, resulting in the proportional enrichment of certain LCPUFA, such as AA and DHA in fetal as compared with maternal compartments *(125)*.

We have recently found that the concentration of PUFA in plasma lipoproteins in pregnant women during the third trimester of pregnancy is much greater than that in NEFA *(7)* (Fig. 5*)*, and previous evidence indicates that circulating triglycerides contribute to plasma fetal fatty acids in the rat *(126)*, rabbit *(90)*, guinea pig *(127)*, and human *(128)*. Therefore, although lipoprotein triglycerides do not directly cross the placental barrier, as already mentioned, the placenta has mechanisms to release fatty acids circulating in maternal plasma lipoproteins into the fetus.

Glycerol

Plasma glycerol levels are consistently elevated during late pregnancy *(22,129)*. Their values are higher in the mother than in the fetus, although with some interspecies differences. The maternal/fetal glycerol gradient is greater in those species with an epitheliochorial placenta *(130)*, as is the case of ruminants, than in those with a hemochorial placenta *(131, 132)*. Although having low molecular weight and uncharged structure, glycerol would be adequate for easy placental transfer. However, the actual amount of glycerol that crosses the placenta is much lower than other metabolites with similar molecular characteristics such as glucose or L-alanine *(2, 66,133)*. Different from these two metabolites, transfer of placental glycerol is carried out by means of a simple diffusion mechanism *(2)*, and the reason for its small placental transfer may reside in both its low concentration and its short half-life in maternal plasma, which limits its availability. This hypothesis is supported by the fact that hepatectomy and nephrectomy in pregnant rats causes a smaller increase in plasma glycerol than in nonpregnant rats. This difference is not a consequence of reduced lipolytic activity in the pregnant rat because plasma NEFA increases even more than in nonpregnant animals. Fetal plasma glycerol appears higher in hepatectomized and nephrectomized rats than in controls, indicating a higher transfer to the fetus in the former *(23)*.

Thus, transfer of placental glycerol seems to be limited by the effective and rapid utilization of this substrate through other pathways, such as gluconeogenesis *(30,134)* and glyceride glycerol synthesis *(132)*, and therefore its low plasma concentration and very active kinetics impede the formation of the adequate gradient to create the appropriate driving force for its placental transfer.

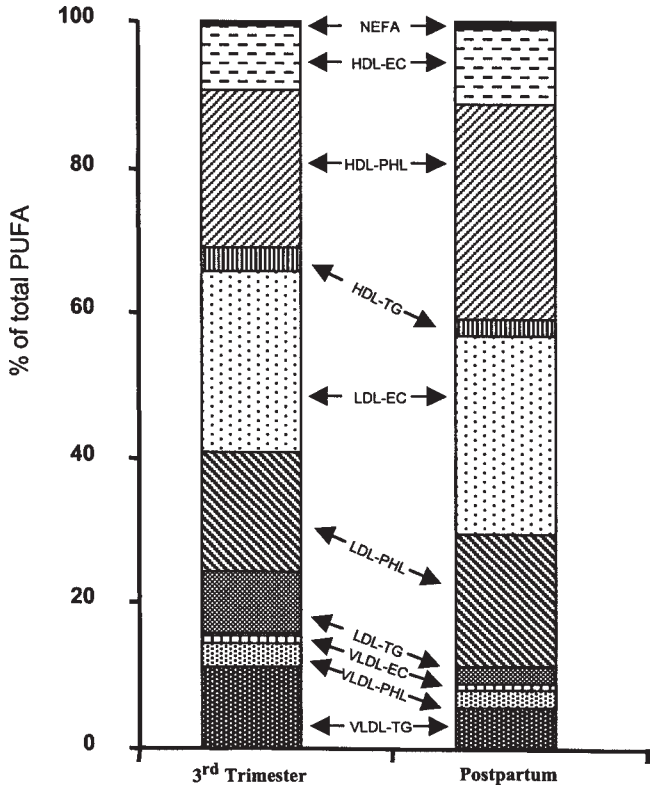

Fig. 5. Proportional distribution of PUFA in plasma NEFA and lipoprotein fractions in women during the third trimester of pregnancy and at postpartum (2–6 mo). Lipoproteins were isolated by sequential ultracentrifugation and PUFA are quantified as previously described *(73,206).* EC, esterified cholesterol; PHL, phospholipids; TG, triglycerides.

Ketone Bodies

In the third trimester of pregnancy, under fed conditions, plasma ketone body levels remain low, but they greatly increase compared to nonpregnant conditions under fasting *(32,33,135)* or in diabetes *(73,136,137)*, as a consequence of enhanced adipose tissue lipolysis, which accelerates the delivery of NEFA to the liver and enhances ketogenesis.

As mentioned, besides being used by maternal tissues as alternative substrates for glucose, ketone bodies can easily cross the placenta and be used as fuels and lipogenic substrates by the fetus. Maternal hyperketonemia in the poorly controlled diabetic patient and secondary transfer of excessive arrival of ketone bodies to the fetus seem to be responsible for major damage there *(138)*, increasing stillbirth rate, incidence of malformations, and impaired neurophysiologic development *(139–141)*.

The transfer of ketone bodies across the placenta occurs either by simple diffusion or by a low-specificity carrier-mediated process *(35,130)*, whose efficiency varies among species, being much lower in the ruminant than in the nonruminants. This causes major differences in the maternofetal

gradient for ketone bodies, which is above 10 in ruminants *(138,142)*, around 2 in humans *(143)* and 1 in the rat *(144, 145)*, indicating that the amount of ketone bodies crossing the placenta is much lower in ruminant than in nonruminant species. A similar relationship may be proposed for the contribution of ketone bodies to fetal oxidative metabolism, which is only 2 to 3% in the case of sheep *(146)*. In the rat, however, 3-hydroxybutyrate may replace glucose deficit in the placenta, as well as in fetal brain and liver during fasting hypoglycemia *(36)*, suggesting a much greater contribution of ketone bodies to the fetal oxidative metabolism.

The activity of ketone body metabolizing enzymes is present in fetal tissues (brain, liver, and kidney) *(36,37,139, 147)* and can be increased by conditions of maternal ketonemia such as starvation, during late pregancy *(148)* or high-fat feeding *(149)*. These changes may represent an important adaptation to guarantee brain development under these conditions of limited availability of other substrates and may represent a special preservation of fetal brain compared with other fetal organs.

Therefore, in nonruminant species there is evidence for an effective placental ketone body transfer and its efficient use by the fetus as substrates for both oxidation and lipogenesis. Although these processes are concentration dependent, their quantitative contribution to fetal metabolism is only relevant under conditions of maternal hyperketonemia (e.g., starvation, high-fat intake, and diabetes) *(36)*.

Cholesterol

Cholesterol plays a key role in embryonic and fetal development. It is an essential component of cell membranes, where it contributes to membrane fluidity and passive permeability by interacting with phospholipids and sphingolipids *(150)*. Cholesterol is the precursor of bile acids and steroids, and in the fetus at late pregnancy there is an intense synthesis of glucocorticoids in the adrenals. Cholesterol is also required for cell proliferation *(151,152)* and plays important roles in cell differentiation and cell-to-cell communication *(153)*. In addition, cholesterol and its oxidative derivatives, oxysterols, are key regulators of different metabolic processes *(154–156)*. The demands for cholesterol in the embryo and the fetus are therefore relatively high. The fetus may obtain cholesterol from endogenous synthesis as well as from the yolk sac and the placenta.

Placental transfer of maternal cholesterol has been shown to be effective in different species, such as rat *(157)*, guinea pig *(158)*, and rhesus monkey *(159)*, although the estimated contributions of maternal cholesterol to the fetus were quite variable, mainly owing to methodologic reasons. Cholesterol synthesis in fetal tissues, and especially in fetal brain, is highly active in different species, even higher than in maternal tissues when expressed per mass unit *(160–164)*. These findings are consistent with the high level of mRNA expression of different enzymes involved in cholesterol synthesis *(165)* and the high activity of 3-hydroxy-3-methyl glutaryl coenzyme A reductase, the rate-limiting enzyme of cholesterol synthesis, in fetal tissues *(166,167)*.

In the rat, it has been shown that the fetus receives little or no cholesterol from the mother, satisfying its need for cholesterol through endogenous synthesis *(163,164)*. Feeding pregnant rats with cholesterol, which resulted in increased plasma cholesterol concentration and reduced maternal cholesterol synthesis, did not affect any of these parameters in the fetus *(160,161,168,169)* or fetal development *(170)*. All of these findings led to the conclusion that in the rat, during late gestation, fetal cholesterol originates mainly from endogenous *de novo* synthesis rather than from placental transfer. However, during the early stages of gestation, maternal cholesterol contributes substantially to fetal cholesterol. This is why treatments with an inhibitor of Δ6-reductase, AY 9944, result in fetal teratogenesis, but simultaneous administration of oral cholesterol during early pregnancy completely prevents this effect *(171–173)*. These findings indicate that during early pregnancy in the rat, maternal cholesterol reaches the fetus and plays an important physiologic role.

In humans, it has been found that umbilical venous levels of HDL-, LDL-, and total-cholesterol concentrations were higher than in umbilical arterial plasma at term, indicating the delivery of cholesterol from the placenta to the fetus, but the contribution of this cholesterol to the fetal plasma cholesterol pool was very small *(174)*. Comparison of mater-nal lipoprotein-cholesterol levels and those in mixed umbil-ical cord blood cholesterol gave either a positive correlation *(175,176)* or no correlation between these values *(174,177–179)*. Gestational age could influence these comparisons, since plasma fetal cholesterol levels have been found higher in 5- than in 7-mo-old fetuses *(8)*. In fetuses younger than 6 mo, plasma cholesterol levels are significantly correlated to the maternal ones *(8)*, suggesting that maternal cholesterol actively contributes to fetal cholesterol in early gestation.

The presence of several lipoprotein receptors in the placenta *(84,180)* and, to a lesser extent, in the yolk sac *(181)* allow these tissues to take up cholesterol from maternal lipoproteins, although the contribution of this process to the export of cholesterol to the fetus remains to be clarified.

Role of Dietary Fatty Acids in the Offspring

Normal fetal development needs not only the EFA but also their LCPUFA derivatives to support the synthesis of structural lipids *(182–185)*. Both term and preterm infants seem to be able to form AA (20:4ω-6) from linoleic acid (18:2ω-6) and DHA (22:6ω-3) from α-linolenic acid (18:3ω-3), which are their respective EFA precursors *(186–191)* (Fig. 6); however, the degree to which the fetus is capable of fatty acid desaturation and elongation is not clear. Although fetal baboons have been shown to effectively synthesize both AA

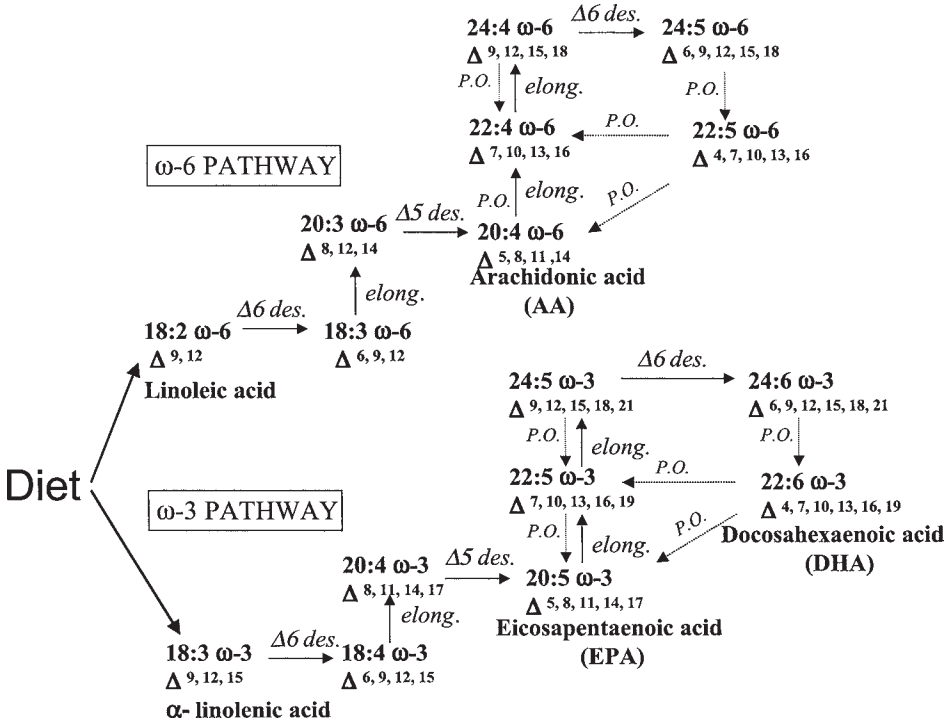

Fig. 6. Schematic representation of desaturation and elongation of dietary essential fatty acids, as precursors of ω-6 and ω-3 pathways. des., desaturase; elong., elongase; P.O., peroxisomal oxidation.

(20:4ω-6) and DHA (22:6ω-3) from their respective EFA precursors *(192,193)*, in the newborn infant during the first week of life, the endogenous synthesis of AA seems to contribute very little to the plasma AA pool *(190)*, the limiting factor being a low Δ^5 desaturation activity.

During gestation, a reduced nutritional status with respect to EFA has been correlated to reduced neonatal growth *(194)*, and plasma levels of LCPUFA have been consistently correlated between the mother and fetus or newborn in untreated healthy women *(195–197)*. After fish oil supplementation during pregnancy, increments in DHA levels have been found in mothers and newborns *(198,199)*. Since these findings showed the important role of dietary fatty acids during pregnancy in controlling the supply of LCPUFA to the fetus and newborn, supplementation with oils rich in these fatty acids has been advised during the last trimester of pregnancy *(198,199)*. However, the competitive inhibition of the Δ^6 and Δ^5 desaturases that control the conversion of EFA into LCPUFA throughout the ω-3 and ω-6 pathways, caused by an excess of specific fatty acids, may inhibit the synthesis of certain LCPUFA that could be essential for fetal growth *(200)*. In fact, excessive intake of safflower, sunflower, or corn oils may inhibit Δ^6 desaturase as a consequence of their abundance in linoleic acid (18:2ω-6), inhibiting the synthesis of DHA (22:6ω-3) from its parent EFA precursor, α-linolenic acid (18:3ω-3). An excess of linoleic acid has also been shown to decrease the formation of AA (20:4ω-6) *(201–205)*. In addition, when fish oil was consumed, low plasma AA levels were found *(200,206)*. This effect was caused by the abundance of both EPA (20:5ω-3) and DHA (22:6ω-3) in this oil. These fatty acids are known to specifically inhibit Δ^6 desaturase activity *(207,208)*, although Δ^5 and Δ^9 desaturase activities were also decreased in rats fed fish oil *(209)*.

The inhibitory effects of an excess of certain dietary fatty acids on LCPUFA synthetic pathways may acquire major relevance during the perinatal period, where the AA has been correlated to body weight in preterm infants *(210–212)*. Adverse effects of low AA concentration in blood on growth during infancy have also been reported *(210,213,214)*.

When polyunsaturated fatty acids (PUFA) intake is increased, the PUFA content of the LDL particles increases concordantly *(215,216)*. The in vitro susceptibility of LDLs to undergo oxidative modification was reported to increase with diets rich in ω-6 PUFA *(215,217,218)*. An increase in plasma thiobarbituric acid reactive substances (TBARs) was also found after dietary periods of ω-6 PUFA enrichments *(219)*. Whether a diet high in ω-3 PUFA increases lipid peroxidation is controversial *(220,221)*. Whereas several studies in humans have shown that dietary supplementation with fish oil rich in ω-3 PUFA does not increase in vivo lipid peroxidation *(222–225)*, other studies in rats and in cell culture have shown that this same treatment reduces the antioxidant capacity *(206,226)* and enhances susceptibility to oxidative damage *(227–229)*. Increased reactive oxygen species and lipid peroxidation resulting in fetal damage, as well as its reversion by vitamin E treatment, have been

experimentally shown to take place in diabetic pregnancy *(230–235)*. However, it is not yet clear whether oxidative stress plays any role in the development of complications in diabetic patients *(236)*. In addition, recently, it has been shown that treating diabetic children with high doses of antioxidative agents, including vitamin E, has no effect on the preservation of β-cell function or on metabolic balance *(237)*. In fact, as recently reviewed *(238)*, some studies suggest a potential usefulness of vitamin E in the prevention of mutagenic effects caused by genotoxic free radicals, whereas other studies report none.

The negative effect of high dietary fish oil intake during pregnancy on offspring could be mediated either by the decreased AA levels *(239,240)* or by an enhanced consumption of α-tocopherol owing to the high LCPUFA content in fish oil. In contrast with fish oil, dietary olive oil protects the ω-3 PUFA series *(241)*, does not affect AA concentrations *(242–244)*, and is much more resistant to lipid peroxidation *(219,245,246)*. Thus, a comparative study of these variables in rats fed a diet supplemented with either 10% fish oil or olive oil as the only nonvitamin lipid during pregnancy and lactation was carried out *(206)*. A decrease in both AA and α-tocopherol concentrations as well as a delayed postnatal development was found in the offspring of rats fed the fish oil–rich diet *(206)*. The study was extended to determine whether dietary supplementation with either vitamin E or γ-linolenic acid (18:3ω-6), as a precursor of AA, could ameliorate these changes. Both AA concentrations and postnatal development indexes, although not α-tocopherol concentrations, were recovered when the fish oil diet was supplemented with γ-linolenic acid. However, postnatal development indexes were not recovered when the fish oil–rich diet was supplemented with sufficient exogenous vitamin E to normalize α-tocopherol levels *(206)*. It was therefore concluded that low AA acid rather than α-tocopherol was responsible for the delayed postnatal development in the offspring of rats receiving a diet supplemented with fish oil instead of olive oil during pregnancy and lactation.

In conclusion, since on the one hand, the safety of high intakes of LCPUFA during pregnancy is still unclear and, on the other, the risks and benefits of supplements with vitamin E are not clearly determined either, additional research is indicated before recommendations to increase LCPUFA intake or to implant vitamin E treatment in pregnancy are made.

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