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Maternal Lipid Metabolism and Placental Lipid Transfer

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Key Words
Adipose tissue · Lipoproteins · Placenta · Polyunsaturated fatty acids · Pregnancy

Abstract
During early pregnancy, long-chain polyunsaturated fatty acids (LC-PUFA) may accumulate in maternal fat depots and become available for placental transfer during late pregnancy, when the fetal growth rate is maximal and fetal requirements for LC-PUFAs are greatly enhanced. During this late part of gestation, enhanced lipolytic activity in adipose tissue contributes to the development of maternal hyperlipidaemia; there is an increase in plasma triacylglycerol concentrations, with smaller rises in phospholipid and cholesterol concentrations. Besides the increase in plasma very-low-density lipoprotein, there is a proportional enrichment of triacylglycerols in both low-density lipoproteins and high-density lipoproteins. These lipoproteins transport LC-PUFA in the maternal circulation. The presence of lipoprotein receptors in the placenta allows their placental uptake, where they are hydrolysed by lipoprotein lipase, phospholipase A_2 and intracellular lipase. The fatty acids that are released can be metabolized and diffuse into the fetal plasma. Although present in smaller proportions, maternal plasma non-esterified fatty acids are also a source of LC-PUFA for the fetus, their placental transfer being facilitated by the presence of a membrane fatty acid-binding protein. There is very little placental transfer of glycerol, whereas the transfer of ketone bodies may become quantitatively important under conditions of maternal hyperketonaemia, such as during fasting, a high-fat diet or diabetes. The demands for cholesterol in the fetus are high, but whereas maternal cholesterol substantially contributes to fetal cholesterol during early pregnancy, fetal cholesterol biosynthesis rather than cholesterol transfer from maternal lipoproteins seems to be the main mechanism for satisfying fetal requirements during late pregnancy.

Introduction

Maternal body fat accumulation during early pregnancy allows the accumulation of an important store of long-chain polyunsaturated fatty acids (LC-PUFA) derived from both the maternal diet and maternal metabolism. These stores become available for placental transfer during the last third of gestation, when the fetal growth rate is maximal and fetal requirements for these essential fatty acids are greatly enhanced. In this late stage of gestation, lipolytic activity in adipose tissue is increased. The fatty acids that are released, as well as fatty acids from dietary lipids and hepatic overproduction of triacylglycerol, are responsible for increasing the amount of triacylglycerol, in maternal circulating lipoproteins. Although maternal plasma lipoproteins do not directly cross the placental barrier, hypertriacylglycerolaemia in pregnancy

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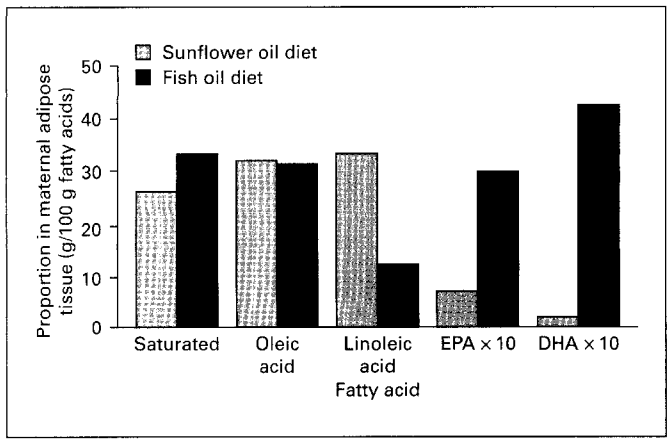

Fig. 1. Effect of a semisynthetic diet containing 10% fish oil or sunflower oil as the only non-vitamin lipid during pregnancy on the profile of adipose tissue fatty acids at day 20 of gestation in rats. Details of diet composition and fatty acids analysis as reported in [7]. EPA = Eicosapentaenoic acid; DHA = docosahexaenoic acid.

plays a key role in the availability of fatty acids for the fetus: lipoprotein receptors in placental cells allow the uptake and release of their lipid components to the fetus. Non-esterified fatty acids (NEFA) are able to cross the placenta without prior modification, while fatty acid-binding proteins in the placenta are responsible for the preferential transfer of certain LC-PUFA. Cholesterol can also be transferred by the placenta, although the efficiency of this process seems to depend on gestational age.

In this article, we will examine the mechanisms underlying materno-fetal lipid transfer, emphasizing the role of maternal diet in the availability of LC-PUFA to the fetus.

Adipose Tissue Metabolism

Accumulation of Body Fat during Early Pregnancy

During the first two-thirds of gestation, the maternal body accumulates fat [1, 2] as a result of hyperphagia [3], enhanced lipogenesis [4] and unmodified or even increased lipoprotein lipase (LPL) activity [5, 6]. This enzyme is present in the capillary endothelium of extrahepatic tissues and hydrolyses triacylglycerols in plasma triacylglycerol-rich lipoproteins. The hydrolytic products, fatty acids and glycerol, are taken up by adipose tissue. By this mechanism, dietary LC-PUFA are stored in maternal adipose tissue during pregnancy. In fact, when female rats are fed during pregnancy with a semisynthetic diet containing 10% sunflower oil, which is rich in linoleic acid (18:2 ω-6), as the only non-vitamin lipid component, this fatty acid becomes the most abundant LC-PUFA in adipose tissue in late pregnancy (fig. 1). Similarly, when rats are fed with the same diet but containing 10% fish oil, which is rich in docosahexaenoic acid (22:6 ω-3) and eicosapentaenoic acid (20:5 ω-3), rather than sunflower oil, these two fatty acids become the most abundant in maternal adipose tissue. A similar increased accumulation of ω-3 fatty acids in adipose tissue was found at day 20 of pregnancy in rats that were fed the fish oil diet only during the first 12 days of gestation and were fed a control diet rich in olive oil during the second half of gestation (data not shown). These findings demonstrate the efficient accumulation of LC-PUFA from dietary fatty acids in maternal adipose tissue during early pregnancy.

Adipose Tissue Metabolism during Late Pregnancy

The tendency to accumulate fat stops during late gestation [1, 8] because maternal lipid metabolism changes to a catabolic condition. This is shown by increased lipolytic activity in adipose tissue [9] and reduced uptake of circulating triacylglycerols [10], secondary to decreased adipose tissue LPL activity [6, 11]. Products of adipose tissue lipolysis – that is, NEFA and glycerol – are mainly transported to the maternal liver. There, after being converted into their active forms, acyl-CoA and glycerol-3-phosphate, respectively, they are re-esterified for the synthesis of triacylglycerols, which are released into the circulation as part of very-low-density lipoproteins (VLDL). The insulin-resistant condition normally present during late pregnancy contributes to these changes, due to the well-known inhibitory effects of insulin on lipolytic activity and its enhancing effects on LPL activity in adipose tissue. The enhanced oestrogen concentration during late pregnancy seems, however, to be the major activator for the increased production of hepatic VLDL.

Under fasting conditions, lipolysis in maternal adipose tissue increases markedly and the lipolytic products are used in the resynthesis of triacylglycerols [12]. Additionally, glycerol may be used preferentially for gluconeogenesis, whereas NEFA are used for ketogenesis. The efficient placental transfer of the newly formed glucose and ketone bodies may be of major importance to the fetus under such fasting conditions. Furthermore, the enhanced release of LC-PUFA from maternal adipose tissue under fasting conditions allows their increased concentration in the maternal circulation and makes them available to the fetus.

Maternal Hyperlipidaemia

Maternal hyperlipidaemia is one of the most consistent and striking changes to take place in lipid metabolism during late pregnancy. It mainly corresponds to increases in plasma triacylglycerols, with smaller rises in phospholipid and cholesterol concentrations. Both triacylglycerol and cholesterol levels in VLDL, low-density lipoproteins (LDL) and high-density lipoproteins (HDL) are higher in pregnant women in the third trimester of pregnancy than in non-pregnant women. The triacylglycerol/cholesterol ratio remains stable in VLDL but increases in both LDL and HDL [13].

The mechanisms responsible for these changes in the maternal lipoprotein profile during pregnancy are summarized in figure 2. The increased lipolytic activity in adipose tissue during late gestation enhances the production of VLDL by the liver, which, together with the decreased removal of VLDL from the circulation as a consequence of the reduced LPL activity in adipose tissue, results in augmented circulating levels of VLDL. The enrichment in triacylglycerols of both LDL and HDL seems to be the result of two additional mechanisms. First, during mid-gestation there is an increase in cholesterol ester transfer protein activity, which mediates the transfer of triacylglycerols from VLDL to the higher-density lipoproteins (LDL and HDL) in exchange for esterified cholesterol [6, 14]. Secondly, a decreased hepatic lipase activity [6, 15] reduces the conversion of buoyant triacylglycerol-rich HDL_{2b} into the smaller, denser and triacylglycerol-poor HDL_3 particles, allowing the proportional accumulation of the former [6].

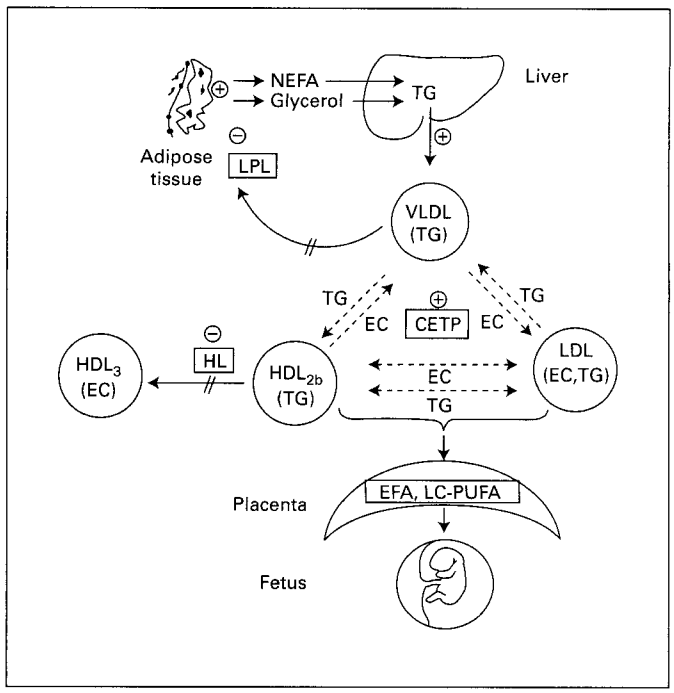

Fig. 2. Schematic representation of the relationship of adipose tissue lipolytic activity with lipoprotein metabolism during late pregnancy and its role as a source of essential fatty acids (EFA) and long-chain polyunsaturated fatty acids (LC-PUFA) for the fetus. EC = Esterified cholesterol; CETP = cholesterol ester transfer protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LPL = lipoprotein lipase; NEFA = non-esterified fatty acids; TG = triacylglycerols; VLDL = very-low-density lipoprotein.

Placental Transfer of Lipid Metabolites

Maternal Hyperlipoproteinaemia as a Source of Fetal Fatty Acids

Essential fatty acids derived from the maternal diet are transported as triacylglycerols in triacylglycerol-rich lipoproteins in maternal plasma. There is no direct placental transfer of maternal lipoproteins [13], yet they must be made available to the fetus. The presence of VLDL-, LDL-, HDL- and scavenger-receptors as well as LDL receptor-related proteins allows these lipoproteins to be taken up by the placenta. In addition, placental tissue expresses LPL, phospholipase A_2 and intracellular lipase activities (for a recent review, see [13]). Maternal triacylglycerols in plasma lipoproteins are therefore either taken up intact by the placenta or are hydrolysed and their constituent fatty acids taken up, where they are re-esterified to synthesize glycerolipids to provide a reservoir of fatty acids [16]. Subsequent hydrolysis of glycerolipids releases fatty acids into fetal plasma, where they bind to a specific oncofetal protein, the α-fetoprotein, and are rapidly transported to the fetal liver.

In pregnant rats at day 20 of gestation, LC-PUFA are mainly transported associated with plasma lipoproteins rather than as NEFA (fig. 3). Similar results were found in humans [17]. When pregnant rats were fed a semisynthetic diet containing 10% olive oil, fish oil, sunflower oil or palm oil, in order to provide a wide variation in their respective plasma fatty acid profiles, a highly significant linear correlation ($n = 33$, $p < 0.001$) between maternal and fetal plasma levels of arachidonic acid (20:4 ω-6, $r = 0.46$), eicosapentaenoic acid (20:5 ω-3, $r = 0.58$) or docosahexaenoic acid (22:6 ω-3, $r = 0.67$) was found. These findings are consistent with the significant correlation between the proportion of certain LC-PUFA in maternal

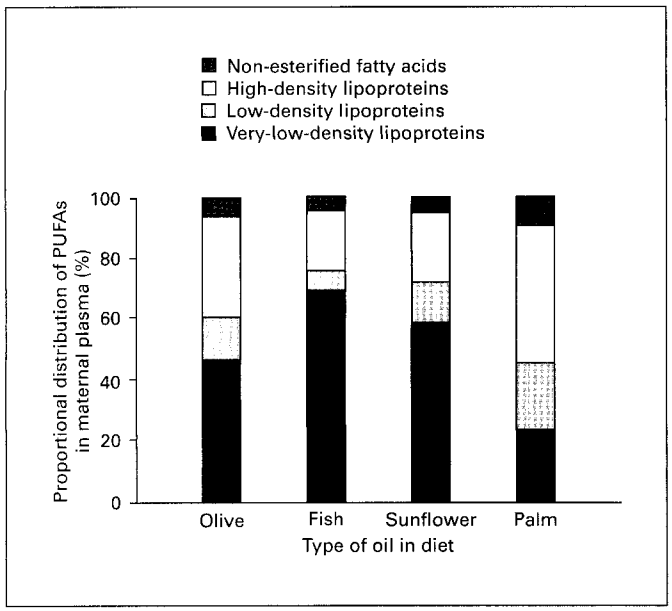

Fig. 3. Proportional distribution of polyunsaturated fatty acids (PUFA) as non-esterified fatty acids and lipoprotein fractions in the plasma of rats at 20 days of gestation fed semisynthetic diets containing 10% of olive oil, fish oil, sunflower oil or palm oil. Treatment of the rats as reported in [7]. Lipoproteins were purified by sequential ultracentrifugation and PUFA quantified as previously described [6, 7].

plasma and cord plasma triacylglycerols during late gestation in humans [18]. Thus, maternal hyperlipoproteinaemia seems to play a key role in the availability of LC-PUFA to the fetus, which is essential for normal fetal development.

Transport of NEFA

Although smaller in proportion to lipoprotein triacylglycerols (fig. 3), maternal plasma NEFA are also a source of LC-PUFA for the fetus. The presence of a membrane fatty acid-binding protein in human placenta [19] allows the preferential placental uptake and transfer of certain LC-PUFA to the fetus. This is combined with intrinsic placental fatty acid metabolism, including the conversion of certain fatty acids to prostaglandins, incorporation into membrane phospholipids, oxidation and synthesis, all of which determine the actual rate of placental fatty acid transfer and its selectivity.

Glycerol

The active lipolytic activity of maternal adipose tissue causes consistent elevation of plasma glycerol concentrations during late gestation. Although experimental data on placental glycerol transfer are scarce, in the rat it has been shown to be much lower than for other metabolites with similar characteristics, such as glucose or *L*-alanine [20]; in humans, it has not been possible to detect glycerol transfer between the mother and fetus, despite its favourable gradient [21]. Placental glycerol transfer could be accomplished by simple diffusion, but the accelerated turnover of maternal glycerol, which facilitates its rapid conversion into glucose by the liver and kidney cortex, limits the availability of sufficient glycerol molecules for transfer to the fetus.

Ketone Bodies

Although under normal conditions, plasma ketone levels in the fed pregnant mother during late gestation are low, during fasting or in diabetes they are greatly elevated as a consequence of increased adipose tissue lipolysis and subsequent enhanced delivery of NEFA to the liver. In all species studied, including humans, increments in maternal plasma ketone bodies are accompanied by increments in fetal plasma levels. As fetal liver ketogenesis is practically negligible, these findings indicate an efficient placental transfer of ketone bodies. The process occurs either by simple diffusion or by a carrier-mediated process [22, 23]. The efficiency of carrier-mediated transfer varies among species and is especially high in non-ruminants.

Key enzymes for utilization of ketone bodies and the capacity to oxidize 3-hydroxybutyrate have been found in the brain and other tissues in the human fetus [23]. As shown in brain, liver, placenta and lung from rat fetuses, some tissues use ketone bodies as substrates for fatty acid and cholesterol synthesis [25]. Thus, there is evidence for efficient placental transfer of ketone bodies and for the use of these compounds as substrates for both oxidation and lipogenesis. However, as both the placental transfer and tissue utilization of ketone bodies are concentration dependent, their contribution to fetal metabolism becomes important only under conditions of maternal hyperketonaemia, as is the case during fasting, a high-fat diet or diabetes.

Cholesterol

The demands for cholesterol in the fetus are relatively high, especially during the last third of gestation, when fetal growth reaches its maximal rate. The placental transfer of maternal cholesterol has been shown to be effective in a number of species, although the level of cholesterol biosynthesis by fetal tissues has also been shown to be high. This is particularly the case for fetal brain and liver.

The brain has been shown to be autonomous in cholesterol accretion, whilst in the liver, cholesterol biosynthesis exceeds the need for cholesterol accretion and excess cholesterol is secreted into the plasma for uptake by other developing fetal organs [26, 27].

In human fetal tissues, cholesterol biosynthesis has not been evaluated, for obvious reasons, and comparisons of maternal plasma lipoprotein-cholesterol with umbilical cord blood cholesterol have not always given positive correlations. The stage of gestation could influence these comparisons, as fetal cholesterol levels show a strong inverse correlation with fetal age, and in plasma of fetuses younger than 6 months, although not in the plasma of older fetuses, cholesterol levels are significantly and directly correlated with maternal concentrations [28]. Therefore, available results in humans indicate that at early stages of gestation, maternal cholesterol substantially contributes to fetal cholesterol. At term, the concentration of HDL-, LDL- and total cholesterol in umbilical venous plasma is higher than in umbilical arterial plasma. The presence of several lipoprotein receptors in the placenta, commented on above, supports the ability of the placenta to take up cholesterol from maternal lipoproteins, but the contribution of such cholesterol to the fetal plasma cholesterol pool seems to be very small [29] and the factors that regulate this process remain to be clarified.

Conclusion

During early pregnancy, LC-PUFA derived from the diet are stored in maternal adipose tissue. However, during late pregnancy, enhanced lipid catabolism as a consequence of the insulin-resistant condition causes the development of maternal hyperlipidaemia, which plays a key role in the availability of LC-PUFA to the fetus. As shown in the rat during late pregnancy, fasting enhances breakdown of fat depots and leads to an exaggerated hyperlipidaemia [30, 31], which may cause an oxidative stress condition. In humans, the nutritional status of the mother is the most important factor leading to intrauterine growth retardation (IUGR) [32]. Besides, conditions of undernourishment have been associated with increased lipid peroxidation and reduced activity of the free oxygen radical scavenger system in babies born SGA [33]. It is not known whether oxidative stress is a cause or effect of IUGR and, although altered transfer of fatty acids throughout the placenta could contribute to oxidative stress in undernourished mothers, an adequate availability of LC-PUFA to the fetus thanks to the development of maternal hyperlipidaemia is clearly needed to preserve normal fetal growth.

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