In: "Fetal and Neonatal Physiology", R.A. Polin & W.W. Fox, eds. W.B. Saunders Co., Philadelphia, 2nd edition, vol. 1, pg.447-458, 1998.

Chapter 45

Maternal-Fetal Transfer of Lipid Metabolites

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Major changes in maternal lipid metabolism during gestation greatly modify the concentration and distribution of circulating lipid components. These changes control availability of lipid metabolites to the fetus even though some of the components do not directly cross the placental barrier. This is the case for maternal plasma lipoproteins; their profile during pregnancy differs markedly from that in the nonpregnant condition, and although no evidence exists for their transfer to the fetus, the placenta cells have lipoprotein receptors that allow the uptake and release of their products to the fetus. Other products of maternal lipid metabolism, however, such as free fatty acids (FFA), glycerol, and ketone bodies, are able to cross the placenta directly and are therefore available to the fetus without prior modification. Although the efficiency of transfer across the placenta differs for each of these metabolites, the major force controlling their actual transfer is the maternal/fetal concentration gradient.

CHANGES WITH GESTATION IN THE LIPOPROTEIN PROFILE

Maternal hypertriglyceridemia is one of the most striking changes to take place in lipid metabolism during gestation. The increase in plasma triglycerides during pregnancy is greater than the increases in phospholipids and cholesterol,[1,2] and more triglycerides are found in all the lipoprotein fractions.[3-6] As shown in Figure 45–1, although both triglycerides and cholesterol increase during gestation, the triglyceride/cholesterol ratio remains stable in very low density lipoproteins (VLDL) despite a significant increase in both low density lipoproteins (LDL) and high density lipoproteins (HDL). An examination of different HDL subclasses indicates that the rise in triglyceride-enriched HDL_{2b} is mainly responsible for the changes in HDL levels, whereas the small HDL_3 fractions become less abundant.[7] The mechanisms responsible for these changes are summarized in Figure 45–2.

The increased adipose tissue lipolytic activity during late gestation[8,9] (which is mediated by an insulin-resistant condition) enhances the availability of substrates for triglyceride synthesis in the liver. This action, together with the stimulating effect of estrogen on VLDL production[10] and the decreased extrahepatic lipoprotein lipase (LPL) activity,[7,11,12] is in part responsible for the augmented circulating levels of VLDL in the woman in late pregnancy. This change in LPL activity corresponds to its decrease in adipose tissue because this is the body tissue that normally has the highest LPL activity and is the only one that shows an intense decrease during late gestation.[13-15,74] The decreased adipose tissue LPL activity is also a consequence of the insulin-resistant state present during late pregnancy.[16,17] Although the abundance of VLDL could justify an enhanced conversion to lipoproteins of higher density, the specific enrichment of the latter seems to be the result of two additional mechanisms (see Fig. 45–2): (1) augmented activity of the cholesteryl ester transfer protein (CETP),[7,18] which mediates the transfer of triglycerides from triglyceride-rich lipoproteins such as VLDL to the higher density lipoproteins LDL and HDL, and (2) decreased activity of hepatic lipase,[7,11] which reduces the conversion of triglyceride-rich HDL_{2b} into the lipid-poor HDL_3. The decreased hepatic lipase activity might be a response to an increase in estrogens during late gestation because these hormones are known to inhibit hepatic lipase activity.[19,20]

The events summarized here are responsible for the sustained hyperlipoproteinemia in the mother during gestation. Because of the impermeability of the placenta to lipoproteins, the precise role that these changes may have on fetal development is as yet unknown; however, the experimental reduc-

Present work was carried out in part with grants from the Fondo de Investigaciones Sanitarias de la Seguridad Social of Spain (No. 92/0407) and EUROLIP (Commission of European Communities, Biomed-1). We thank Carol F. Waren and Rosa Niño for their editorial and secretarial help, respectively.

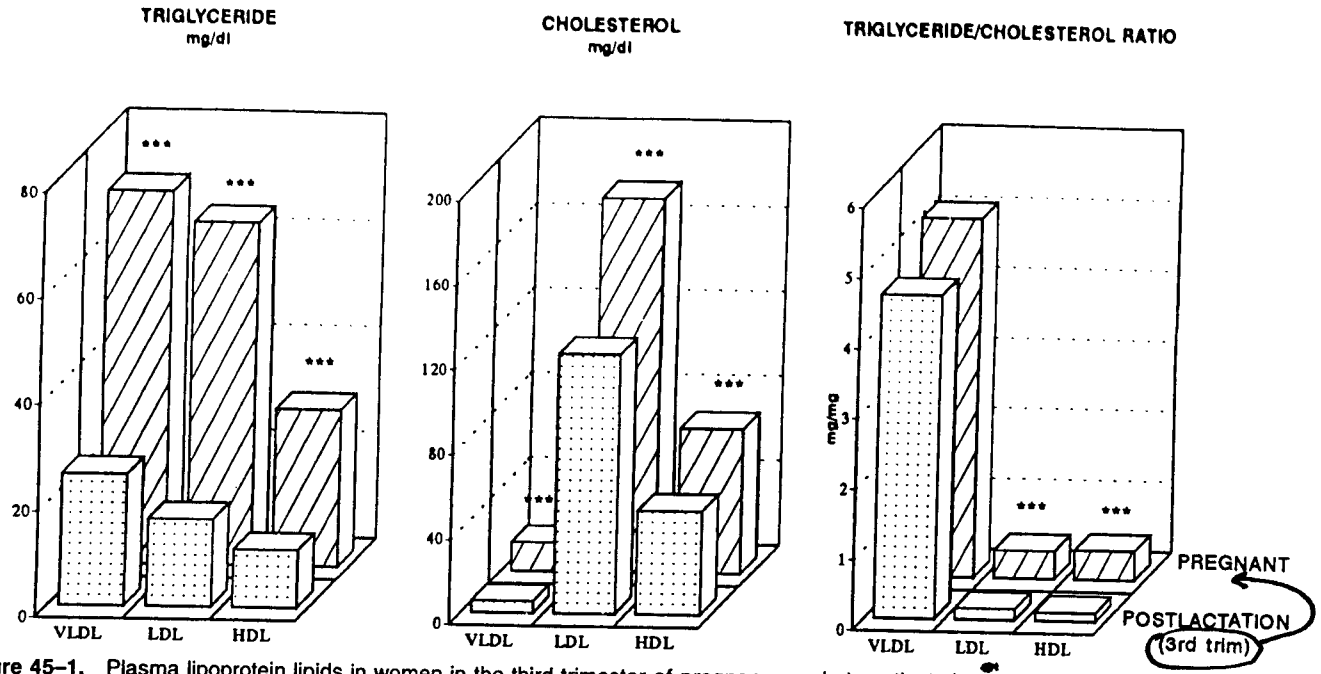

Figure 45–1. Plasma lipoprotein lipids in women in the third trimester of pregnancy and at postlactation. Asterisks indicate significant differences between the two groups.

tion of maternal hyperlipoproteinemia in animals (with cholesterol synthesis inhibitors) has secondary teratogenic effects.[21] The presence of lipoprotein receptors in the placenta ensures the availability of essential lipoprotein components to the fetus and provides a teleologic reason for maternal hyperlipoproteinemia.

UTILIZATION OF LIPOPROTEINS BY THE PLACENTA

The placenta is an active lipoprotein-metabolizing organ. Lipids from lipoproteins are used for energy production, as precursors for steroid hormone synthesis and substrates for the growing fetus. The placental lipoprotein metabolism varies quite markedly among different species.

In mammals, LDL cholesterol is the main precursor for placental steroid hormone synthesis.[22,23] The human placenta manufactures 400 mg of sex steroids daily;[24] most of the cholesterol used for this purpose is derived from lipoprotein cholesterol, and little is manufactured by the placenta itself. LDL is the main donor of cholesterol to cells via the LDL receptor,[25] and this pathway has been demonstrated in human placental cells.[26–28] Binding of radioactive iodine (^{125}I)–labeled LDL to trophoblastic cells is mediated by high-affinity, low-capacity receptors, and LDL stimulates progesterone secretion.[28] Similar findings have been shown in baboon pla-

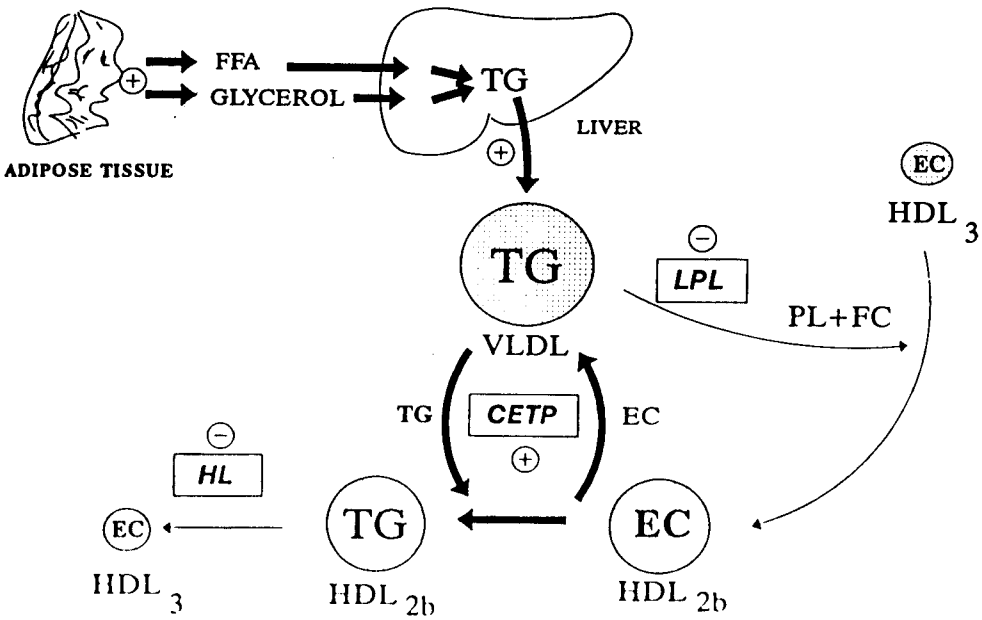

Figure 45–2. Proposed control of major pathways of very low density lipoprotein (VLDL) and high density lipoprotein (HDL) metabolism during late pregnancy. FFA = free fatty acids; LPL = lipoprotein lipase; HL = hepatic lipase; CETP = cholesteryl ester transfer protein; LCAT = lecithin cholesterol acyl transferase; TG = triglycerides; EC = esterified cholesterol; FC = free cholesterol; PL = phospholipids.

centas, in which LDL uptake has been demonstrated to increase during the course of pregnancy;[29] the increase is regulated by the rise in estrogens occurring at that stage of pregnancy.[29] In the human placenta, two mRNA species (approximately 5.3 and 3.7 kb) have been shown to hybridize with the LDL receptor cDNA.[30] The expression of the larger species (which is most common in other cell types)[31] is greater than the expression of the smaller mRNA.[30] The amount of placental LDL receptor mRNA is greatest during the first trimester of pregnancy, when there is a marked increase in the number of placental cells, and a large amount of cholesterol is used for cell membrane synthesis. Subjects with homozygous familial hypobetalipoproteinemia, who lack LDL, can have normal pregnancies, although their placental steroid hormone concentration is decreased.[32]

An alternative source of lipoprotein cholesterol for placental steroid hormone synthesis is derived from HDL cholesterol. In the human trophoblast cell culture model, stimulation of progesterone secretion is stronger when the cells are incubated with HDL_2 than with LDL.[33] The mechanism involved in the efficient use of HDL_2 cholesterol as a substrate for progesterone synthesis does not appear to be receptor mediated but seems to employ direct transfer of free cholesterol from HDL_2 to the trophoblast membrane. Chemical modification of HDL_2 proteins with cyclohexanedione, tetranitromethane, dimethylsuberimidate, or reductive methylation does not affect HDL_2-stimulated progesterone secretion. In contrast to HDL_2, HDL_3 decreases progesterone secretion, which is in accordance with its role in reverse cholesterol transport and, therefore, its contribution to the release of free cholesterol from the cell instead of facilitating its uptake.[27, 33] It has been proposed that HDL_3 may play a role in the regulation of placental lactogen secretion. HDL_3 stimulates placental lactogen secretion in human trophoblast cultures, and the effect is mediated by an increase in cyclic adenosine monophosphate (cAMP).[4]

Cholesterol taken up by placental cells is not only used for steroid hormone synthesis, but also may be transferred to the fetus. There are important differences among mammalian species in the amount of fetal cholesterol derived from maternal lipoprotein cholesterol. In the rhesus monkey, about 42% of fetal cholesterol may be derived from maternal cholesterol,[35] whereas in the rat, the amount of maternal cholesterol reaching the fetus seems to be negligible, and most of the fetal cholesterol comes from its own fetal cholesterol synthesis.[36]

Another potential source of placental cholesterol is derived from oxidized lipoproteins because oxidation seems to be increased during pregnancy.[37–40] Both placental trophoblast and macrophages have scavenger receptors[41–43] that recognize and take up modified lipoproteins (principally oxidized LDL). Because macrophages are localized within the interior of the placental villi,[44] they should lack direct access to circulating oxidized lipoproteins. Trophoblasts compose the surface of the placental villi, however, and are in a position to remove and use oxidized LDL directly should this be present. In a cell culture model, incubation of human trophoblast with oxidized or acetylated LDL led to cholesterol ester accumulation[42] but no progesterone secretion.[42] Therefore, cholesterol derived from oxidized LDL does not seem to have access to the cholesterol pool normally used for steroidogenesis.

The placenta can also use maternal, triglyceride-rich lipoproteins, whether chylomicrons of a dietary origin or VLDL from endogenous synthesis. As with cholesterol, there are wide variations in the utilization of fatty acids from VLDL triglycerides among different mammalian species.[45, 46] Placental utilization of triglycerides appears to be mediated by LPL activity, which has been detected in the placentas of all the species studied, including the human placenta.[47–51] The fatty acids derived from VLDL triglyceride hydrolysis can be taken up by the trophoblasts and reesterified.[52–55] Studies performed in primary cell cultures of human placental trophoblasts and macrophages have demonstrated LPL activity in both cell types.[54] Triglyceride hydrolysis is, however, much higher in macrophages, suggesting that macrophages are the main source of placental LPL activity.[54] The role of placental macrophage LPL in the hydrolysis and uptake of maternal triglyceride-derived fatty acids remains to be determined because these cells are localized in the interstitial space of the placenta and are not in direct contact with maternal blood.[44, 54] The potential use of triglyceride-derived fatty acids for the transfer to the fetus is discussed subsequently.

LIPID METABOLISM IN THE MOTHER AS SOURCE OF FREE FATTY ACIDS, GLYCEROL, AND KETONE BODIES FOR THE FETUS

During the first part of gestation, the maternal body accumulates fat[55–57] as the result of combined effects of hyperphagia, enhanced lipogenesis,[58] and unmodified or even increased extrahepatic LPL activity.[7, 44, 59] The tendency to accumulate fat ceases during late gestation[55, 56, 60, 61] because the maternal lipid metabolism changes to a catabolic condition, as shown by increased adipose tissue lipolysis[8, 15, 62] and reduced uptake of circulating triglycerides.[63] The reduced uptake is secondary to a reduction in adipose tissue LPL activity,[13–15, 74] which is unaccompanied by a change in the enzyme activity of the skeletal muscles.[64] These changes, together with hepatic overproduction of triglycerides[65, 66] and the enhanced absorption of dietary lipids,[67] are responsible for the marked progressive increase in maternal circulating triglycerides occurring during late gestation.[3, 4, 68, 69] The major changes in the maternal lipid metabolism are summarized in Figure 45–3, which diagrams the changes in adipose tissue, liver, and intestinal activity that are responsible for the physiologic increase in circulating FFA, glycerol, and triglyceride-rich lipoproteins (VLDL and chylomicrons). Under fed conditions, maternal ketosis is not different from that in nonpregnant subjects,[70, 71] but it increases markedly under fasting conditions.

With the exception of glycerol used in gluconeogenesis[72, 73] and the circulating triglyceride uptake by the mammary gland before labor,[67, 74, 75] no part of the increase in circulating lipid components in the fed mother during late gestation seems to benefit her metabolic needs directly. This increase, however, may benefit the fetus because this gestational period coincides with the rate of maximal fetal accretion, a time when the substrate, metabolic fuel, and essential component requirements of the fetus are greatly enhanced. The lipid component may also constitute a "floating" fuel store for both mother and fetus, easily accessible under conditions of food deprivation, and explain the well-known finding of enhanced ketogenesis in the mother under fasting conditions.[70, 76–78] This hypothesis is supported by data demonstrating an increased arrival of FFA in the liver as a result of greatly enhanced adipose tissue lipolysis[8, 62] and by studies reporting an increase in liver LPL activity,[14, 79, 80] which facilitates maternal liver use of circulating triglycerides as ketogenic substrates.

The enhanced ketone body arrival in fasted maternal tissues allows the ketone bodies to be used as metabolic fuels and may spare other more limited and essential substrates, such as amino acids and glucose, for transport to the fetus.

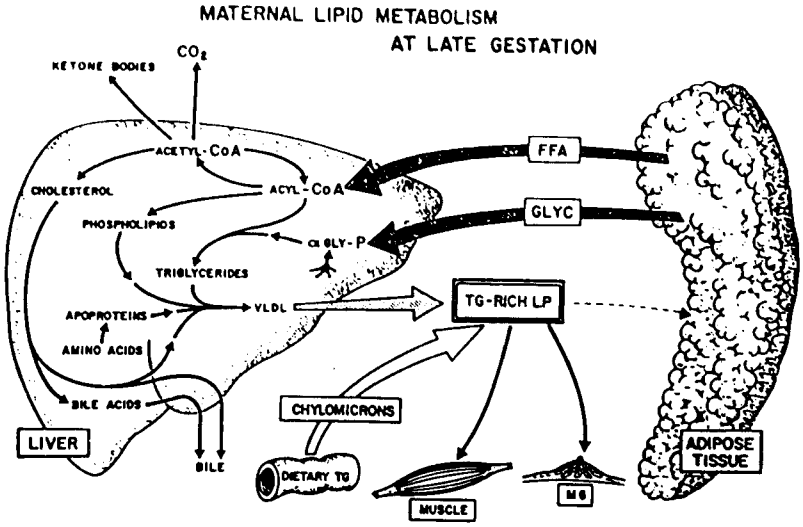

Figure 45–3. Summary of major changes in maternal lipid metabolism at late gestation. FFA = free fatty acids; TG-RICH LP = triglyceride-rich lipoproteins; TG = triglycerides; MG = mammary gland; VLDL = very low density lipoproteins; Glyc = glycerol. (Adapted from Herrera E, et al: Lipid metabolism in pregnancy. Biol Neonate *51*:70–77, 1987. S. Karger AG, Basel.)

The fetus also receives maternal ketone bodies through the placenta, and their use plays an important role in the fetal metabolic economy under conditions of maternal food deprivation. Augmented lipolytic activity also increases maternal circulating glycerol levels.[15, 72] Glycerol can be used as an efficient gluconeogenic substrate[72, 73, 81, 82] and therefore contribute to the maintenance of glucose production for fetal and maternal tissues. Metabolic adaptations found in the mother during starvation are summarized in Figure 45–4. The transfer of glucose, ketone bodies, and amino acids is emphasized in this figure because, quantitatively, they are the major substrates crossing the placenta in this condition.

TRANSFER OF LIPID PRODUCTS TO THE FETUS

This section focuses on the mechanism and control of placental lipid transfer. Understanding FFA, glycerol, and ketone body placental transfer as well as their respective metabolic fates in the fetus provides a clearer insight into the effect on the fetus of these persistently elevated maternal circulating lipid levels.

Figure 45–5 compares plasma levels of these metabolites in virgin as well as 24-hour fasted late pregnant rats and their fetuses. It can be seen that although fetal FFA and glycerol levels are much lower than in their mothers, the concentration of ketone bodies is similar. These maternal/fetal concentration differences probably reflect the efficiency or magnitude of the placental transfer process.

Maternofetal nutrient transfer through the placenta may be accomplished by means of different mechanisms, including facilitated diffusion, active transport, and simple diffusion.[83–86] Simple diffusion seems to be the common and unique mechanism for the lipid-derived moieties, although some specific and differential aspects must be considered. Simple diffusion is carried out from a high to a low concen-

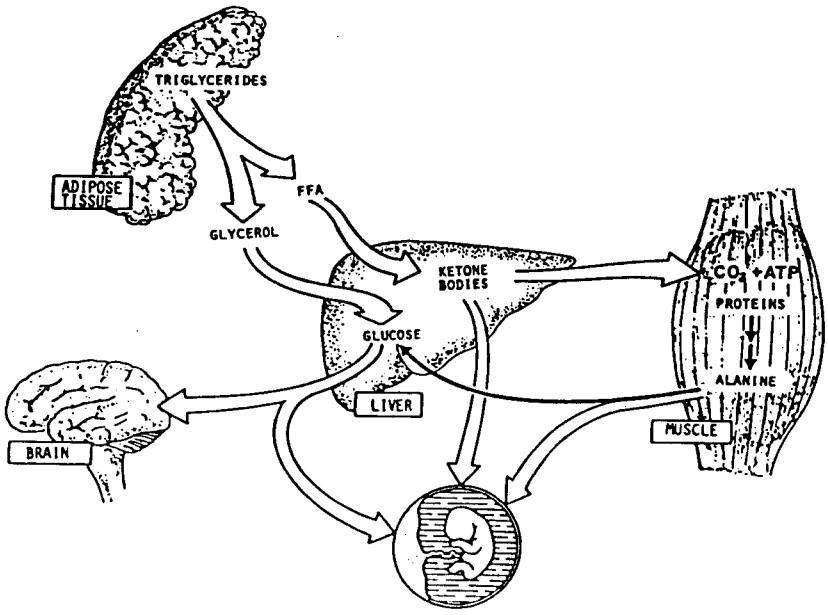

Figure 45–4. Maternal response to starvation. Enhanced adipose tissue lipolysis increases the availability in the liver of glycerol to be used as a preferential substrate for gluconeogenesis and of free fatty acids (FFA) for ketone body synthesis. By this mechanism, the mother conserves other gluconeogenic substrates, such as alanine, and ensures the adequate availability of fuels and metabolites to the fetus. (From Herrera E, et al: Lipid metabolism in pregnancy. Biol Neonate *51*:70–77, 1987. S. Karger AG, Basel.)

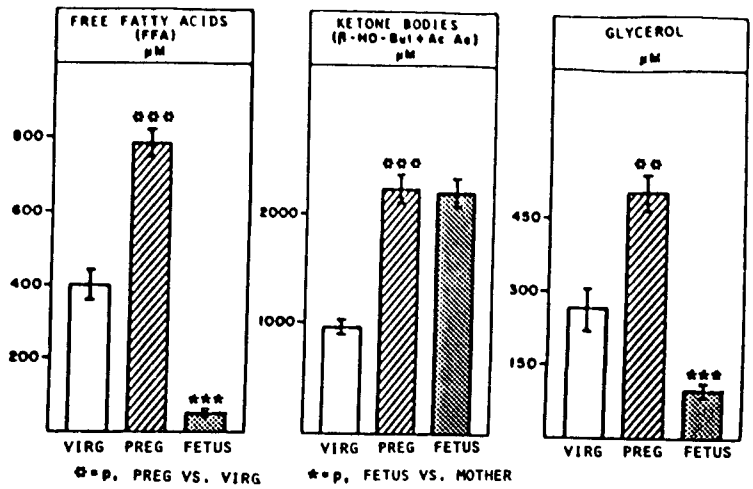

Figure 45–5. Concentration of free fatty acids, ketone bodies, and glycerol in plasma of 48-hour starved virgin rats and 48-hour starved 19-day pregnant rats and their fetuses. (From Herrera E, et al: Lipid metabolism in pregnancy. Biol Neonate *51*:70–77, 1987. S. Karger AG, Basel.)

tration region, and the rate of movement is directly proportional to the concentration gradient as described by Fick's law:

$$J = D\frac{dc}{dx}$$

where J = transfer rate, D = diffusion coefficient, and dc/dx = chemical gradient. The rate of transfer is therefore a direct function of the concentration gradient and decreases with molecular size and hydrosolubility.[87] In the specific condition of the placental transfer, other factors also participate in the efficiency of nutrient transfer,[87–91] such as uterine and umbilical blood flows, intrinsic placental metabolism (utilization versus production); and structural characteristics of the placental barrier. As may be expected, some of these factors, such as blood flow, contribute analogously to the transfer of any nutrient crossing by passive diffusion, but other factors differ with each nutrient and require specific consideration.

Free Fatty Acids

The fetus requires not only essential fatty acids from the mother to support growth[92] and brain development,[93] but also nonessential lipids, which, stored in fetal body fat, become an important substrate during early postnatal life.[94] This is especially true in species such as the guinea pig and human, in which body fat at term represents a substantial percentage of body weight (10% in guinea pig and 16% in human),[95] and *de novo* fatty acid synthesis by fetal tissues cannot fulfill fetal requirements.

Fatty acids, similar to other fats, are relatively insoluble in water and must be transported in the blood either as albumin-bound FFA or in their esterified form as triglycerides, phospholipids, and esterified cholesterol, which are associated with other lipids and proteins in the form of lipoproteins. Maternal FFA, esterified fatty acids that have been hydrolyzed at the placental level, and unmodified lipoproteins are, therefore, the potential sources of the fatty acids that cross to the fetal side.

Early studies in the sheep[96] that measured venous-arterial differences across the umbilical circulation of the fetus *in utero* and across the maternal uterine circulation showed no significant passage of FFA to the fetus and led to the conclusion that FFA did not appear to constitute a significant part of the metabolic fuel supplied by the mother to the fetus.[96] Later studies demonstrated, however, that the net flux of fatty acids from mother to fetus across the placenta varies greatly among species. For example, in species with both maternal and fetal layers in the placenta, such as the sheep, pig, and cat, the net transfer of fatty acid to the fetus is generally small.[97–100]

In contrast, in species such as the rabbit,[101] guinea pig,[102, 103] primate,[104] and rat[105, 106] (in which the placental barrier is formed by only a few layers of fetal origin), the amount of fatty acids crossing the placenta even exceeds that needed to fulfill lipid storage requirements.[107] In these species, the fatty acid mixture entering fetal circulation from the placenta reflects the maternal FFA concentrations of the different fatty acids.[97] Furthermore, maternal dietary manipulation with different oil-enriched diets leads to corresponding changes in the fatty acid composition of the fetus.[108] These observations, therefore, constitute indirect evidence for the transplacental passage of fatty acids from mother to fetus.

As noted earlier, FFA levels in the fetus generally correlate with maternal levels. Arachidonic acid is an interesting exception to this rule in that higher proportions of arachidonic acid have been observed in fetal plasma (compared to maternal plasma) in both ruminant[109] and nonruminant species.[104, 110–112] Because significantly higher proportions of arachidonic acid have been consistently noted in the placenta when compared with the levels in maternal lipid fractions,[109] it has been suggested that placental arachidonic acid synthesis is important in the supply of this fatty acid to the fetus. An active desaturation and elongation system is required to synthesize arachidonic acid from the active form of linoleic acid (linoleyl-CoA). Such a system has been described in the placenta of sheep,[113, 114] and the observation of active incorporation of arachidonic acid into placental phosphoglycerides in both the ovine[115] and the human placenta[116] supports a preferential role for the placenta in the synthesis, selective sequestration, and supply of arachidonic acid to the fetus.

In general, the concentration of FFA in fetal plasma is significantly lower than in maternal plasma, which suggests that the placenta is not freely permeable to the transfer of these compounds. Furthermore, current evidence indicates that fatty acids are not selectively transferred across the placenta, and essential and nonessential fatty acids seem to use a common transfer mechanism. Using *in situ* perfused guinea pig or rabbit placentas, several investigations have demonstrated that, within the physiologic range, the net FFA transfer to the fetus correlates with maternal plasma levels of FFA and that this transfer is regulated by the transplacental concentration gradient.[117–119] Furthermore, during maternal fasting, increased amounts of maternal FFA cross the placenta into fetal circulation and are incorporated into the fetal

stores.[120] These observations suggest that the transfer of FFA across the placenta is mainly by diffusion. Other factors affecting this transfer process are the uterine and umbilical blood flow rates[117, 119, 121] and the fetal plasma albumin concentration.[117, 121, 122] In this respect, the increase in albumin levels throughout the third trimester in the human fetus[123] may increase its FFA supply.

As indicated previously, the amount of fatty acid transferred to the fetus varies considerably among species,[124] and, at the least, it is responsible for the transfer of essential long chain polyunsaturated fatty acids. The authors have studied the placental transfer of different metabolites in the 20-day pregnant rat by infusing radioactive carbon (^{14}C)–labeled palmitic acid through the left uterine artery for 20 minutes. The amount of label appearing in the placentas and fetuses from the left uterine horn was contrasted with that found in those from the right horn.[125] Although the left uterine horn received the tracer directly, it reached the right horn after dilution in the mother's circulation, so the amount of substrate transferred to the fetus can be calculated as a function of the values for the concentration of the studied metabolite in maternal plasma, the difference of radioactivity in fetuses between the left and right uterine horns, and the left uterine blood flow.[126–129] As shown in Figure 45–6, the estimated FFA transfer was above 7 nmol/minute × g fetal body weight, a value that was similar to that estimated by others in the rat using different methods.[130] This transfer of FFA appears to be lower than the level previously found for other compounds in earlier studies: glucose, 127 nmol/minute × g fetal body weight; alanine, 23 nmol/minute × g fetal body weight, but higher than that of glycerol, 1 nmol/minute × g fetal body weight.[129] When the ^{14}C-labeled lipids that had been retained in the placentas after (1-^{14}C)-palmitate infusion were measured, it was found that the level was 99 ± 38 nmol/g/minute, which is much higher than that found in the fetus. Of those ^{14}C-labeled lipids incorporated into the placenta, 49 ± 3% corresponded to esterified fatty acids, indicating that a certain proportion of the FFA that reach the placenta are actively esterified. It is not known whether fatty acid esterification participates in the FFA transfer process, but an active placental capacity to form esterified fatty acids from maternal FFA has also been described in other species[131, 132] as well as in humans.[52, 133] The presence of an active enzymatic glyceride hydrolytic system (phospholipase and triacylglycerol lipase) (ensuring a rapid triglyceride and phospholipid turnover) points to an esterification/hydrolysis cycle in the placental cells as one type of placental FFA transport. Such a system was proposed by Szabo and colleagues[134] and Hummel and associates[135] several years ago.

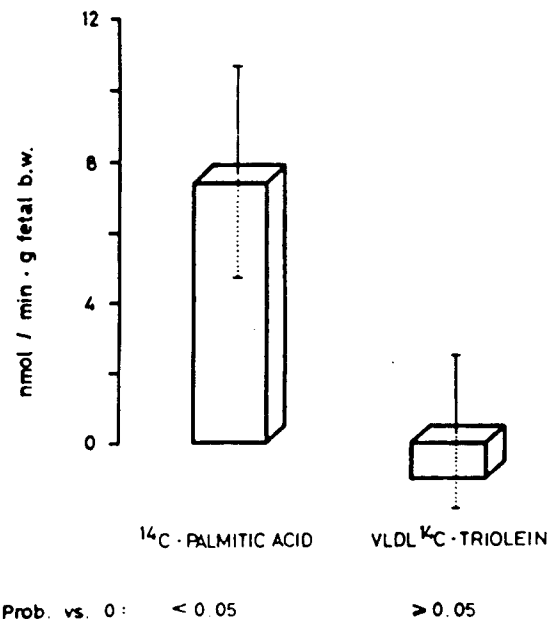

Figure 45–6. Estimation of placental transfer of palmitic acid and VLDL-triolein in the 20-day pregnant rat. Placental transfer to the fetus was determined by measuring the radioactivity appearing in fetuses after infusing each of the ^{14}C-labeled substrates through the left uterine artery and making proper correction of the data for specific activity dilution of the tracer and uterine blood flow, as previously described (see ref. 127).

Maternal plasma triglycerides have been considered as an alternative source of fatty acids for the fetus. Previous evidence indicates that maternal circulating triglycerides contribute somewhat to FFA levels in the fetal circulation of the rat,[47, 136] rabbit,[48] guinea pig,[45, 137] and human.[46] The authors applied the *in situ* uterine artery infusion technique[125] described previously to test the potential transfer of VLDL-^{14}C-triolein across the placenta and its incorporation into fetal lipids.[138] During the 20-minute study, no significant differences were noted in radioactivity incorporated into fetuses from the left horn as compared to those from the right horn. Therefore, the authors concluded that the transfer of fatty acids to the fetus from lipoprotein triglycerides was not significant during the 20-minute study period (see Fig. 45–6). This indicates that lipoprotein triglycerides are not a direct fatty acid source for placental transfer to the fetus; however, the observation that some ^{14}C-radioactivity appeared equally distributed in fetuses from both uterine horns indicated that some of the infused lipoprotein triglycerides were hydrolyzed in maternal peripheral tissues and then were taken up by the placentas as FFA. By following the time course of fetal radioactivity after injecting the mother with labeled chylomicron and VLDL triglycerides, Hummel and associates[136] found that the transfer of triglyceride fatty acids to the rat fetus was half that of maternal FFA. Furthermore, in the *in situ* guinea pig placenta, Lowy and Thomas[137, 139] estimated that the efficiency of triglyceride-derived fatty acid transfer was one-sixth that of FFA transfer. Therefore, available evidence indicates that circulating maternal triglycerides are a quantitatively less important source of fatty acids for the fetus than are circulating FFA.

Because no studies have detected the passage of intact triacylglycerol across the placenta, it is conceivable that esterified fatty acids must first be hydrolyzed before they reach the fetal compartment. As noted earlier, LPL activity has been detected in the placentas of all the species studied.[14, 47–49, 140] Therefore, placental triglyceride hydrolysis by this enzyme and direct transfer of the released nonesterified fatty acids to the fetus are theoretically possible. The authors' studies in the rat and those of Thomas and Lowy with the *in situ* perfused guinea pig placenta, however, have shown that this activity accounts for a small percentage of all the fatty acid transferred to the fetus.[137] These data indicate that, under normal conditions, the contribution of maternal triglyceride-rich lipoproteins that are broken down by LPL in the placenta is of minor quantitative importance as a source of fatty acids for the fetus. Under conditions of exaggerated maternal hypertriglyceridemia, however, this fatty acid supply system from esterified maternal fats may be greatly enhanced in the presence of sustained placental LPL activity, as has been proposed to occur in streptozocin diabetic rats.[47, 51] In that regard, parallel changes in maternal and fetal plasma triglyceride levels have been observed in 20-day pregnant rats subjected to different degrees of diabetes.[12] This finding agrees with the augmented levels of essential fatty acids in

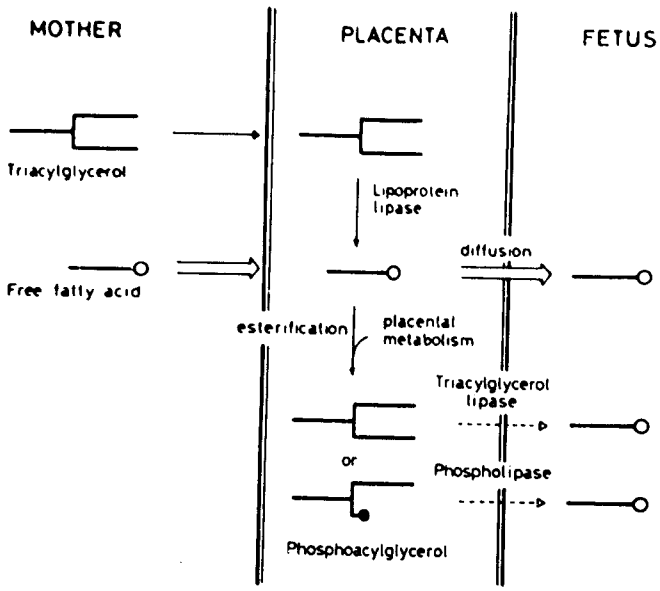

Figure 45–7. Schematic representation of the placental transfer of fatty acids to the fetus.

the circulation of fetuses from hypertriglyceridemic diabetic pregnant rats[47] and suggests either a contribution by maternal triglycerides to fetal lipids or an increase in placental transfer of FFA because of the increased maternal/fetal FFA gradient, or both. These changes may therefore contribute to the well-known fat accumulation in infants of diabetic mothers.

Figure 45–7 outlines the placental role in maternofetal fatty acid transport under normal conditions during late gestation, in which simple direct diffusion constitutes the major process. No attention has been given to modifications of this picture owing to species, length of gestation (which would modify the degree of maternal hyperlipidemia and placental structural and functional maturation), or differences caused by pathologic conditions.

Cholesterol

The fetal cholesterol concentration does not correlate with the maternal cholesterol blood concentration, and, in fact, hypercholesterolemia in the mother does not affect cholesterol levels in the fetus.[141] Early experiments demonstrated that maternal cholesterol was a source of fetal cholesterol to some extent.[35, 142, 143] The observation that feeding the rat mother with cholestyramine—a nonsystemic bile acid sequestrant—induced the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase in fetal liver[144] suggested the possibility that fetal cholesterol homeostasis was strictly dependent on maternal cholesterol. Later studies demonstrated that HMG CoA activation occurred without affecting either fetal plasma cholesterol or fetal cholesterol biosynthesis.[145] In the guinea pig, cholestyramine administration to the mother stimulated ^{3}H-water incorporation into sterols in the maternal liver, a finding that is consistent with the mechanism of action of that drug. In the fetus, however, feeding the mother cholestyramine resulted in reduced rates of cholesterol synthesis at day 40 of gestation and increased fetal cholesterol synthesis at day 60.[146] In contrast, feeding the pregnant guinea pig cholesterol increased the maternal plasma cholesterol concentration and reduced maternal cholesterol synthesis but did not affect any of these parameters in the fetus.[146] Therefore, these studies do not demonstrate a direct contribution of maternal cholesterol to the fetus.

Studies in humans have found positive differences between umbilical venous and arterial plasma levels of HDL-, LDL-, and total cholesterol. These findings suggest that cholesterol derived from maternal plasma can be delivered across the placenta to the fetal compartment.[147] This contribution, however, appears to be of minimal quantitative importance compared to fetal requirements during the course of a normal pregnancy.[36, 147] The high activity of HMG CoA reductase in the fetus[148] and the elevated cholesterol synthesis rate (both of which are higher than in the mother)[146] are consistent with the capacity of all fetal tissues to synthesize cholesterol to meet its requirements for this compound.

Glycerol

As a result of the active lipolytic activity of maternal adipose tissue, plasmatic glycerol levels are consistently elevated during late gestation.[15, 72, 73] Therefore, the values for plasma glycerol are generally higher in the mother than in the fetus (see Fig. 45–5), but there are some interspecies differences. The maternal/fetal glycerol gradient is greater in those species with an epitheliochorial placenta (ruminants)[96, 149] than in those with a hemochorial placenta.[150–152]

There are few experimental data on placental glycerol transfer in any species. Although the molecular characteristics of glycerol are adequate for easy placental transfer (low weight and uncharged molecule), glycerol transfer is notably lower than for other metabolites with similar molecular characteristics such as glucose or L-alanine.[129, 153, 154] In contrast, with the carrier-mediated process used for these two metabolites, placental glycerol transfer is accomplished by simple diffusion.[149, 155] In the sheep fetus, fetal uptake is low, accounting for no more than 1.5% of the total oxygen consumption of the fetus.[96] In humans, it has not been possible to detect a transfer of glycerol from mother to fetus despite its favorable gradient.[150] When comparing different substrates, and by using the *in situ* infused placental technique in the rat, the authors have found that the transfer of glycerol is much lower than that of glucose and alanine and similar to that of FFA.[129] The authors have also found that the fetal-placental unit converts glycerol into lactate and lipids,[152] and this rapid utilization may actively contribute to maintaining the high glycerol gradient consistently found between maternal and fetal blood.[78, 150–153]

Accelerated turnover of maternal glycerol seems to be influenced by the high liver glycerol kinase activity, which facilitates its rapid phosphorylation and subsequent conversion into glucose.[72, 73, 81, 82] Although this mechanism indirectly benefits the fetus by providing glucose (see Fig. 45–4), it may limit the availability of sufficient glycerol molecules for transfer to the fetus. Figure 45–8 summarizes studies that support this hypothesis. Hepatectomy normally results in increased plasma glycerol levels because of a reduction in glycerol utilization secondary to absence of the liver, the major receptor organ for this metabolite.[156] In the case of pregnant rats, hepatectomy and nephrectomy produce a significant, but smaller increase in plasma glycerol levels than in nonpregnant animals. This difference cannot be interpreted as reduced lipolytic activity in the pregnant rat because plasma FFA, the other lipolytic product, increases more than in nonpregnant animals. It might, however, be interpreted as the result of an augmented transfer of glycerol to the fetus because glycerol levels in fetal plasma increase significantly after maternal hepatectomy and nephrectomy.[157]

Therefore, placental glycerol transfer seems to be limited by the effective, rapid utilization of this substrate for gluco-

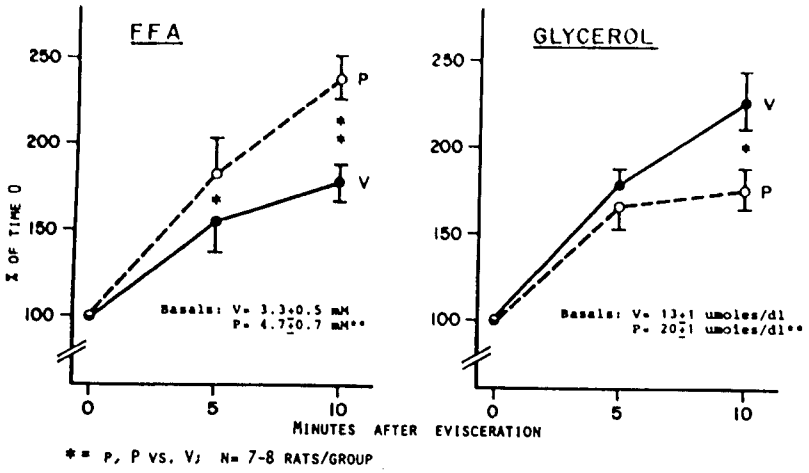

Figure 45–8. Effect of hepatectomy-nephrectomy on plasma free fatty acid and glycerol in virgin (V) and 20-day pregnant rats (P). Experimental details are as indicated in ref. 157.

neogenesis by the liver and kidney cortex of the mother. Although the fetal-placental unit actively uses glycerol (which helps to maintain a favorable transfer gradient), its quantitative and physiologic role in the fetus, except as a preferential substrate for fetal liver glyceride glycerol synthesis,[152] seems to be limited under normal conditions. Under conditions of markedly elevated maternal glycerol levels, however, the placental transfer of glycerol could become an important source of substrates for the fetus.

Ketone Bodies

Although plasma levels of ketone bodies in the fed pregnant mother late in gestation are unchanged under physiologic conditions, under fasting[70, 76, 77, 158–162] or diabetic[3, 163, 164] conditions, they are greatly elevated as a result of increased adipose tissue lipolytic activity and enhanced delivery of FFA to the liver. As noted earlier, when the supply of glucose is limited (e.g., hypoglycemia or reduced insulin levels or sensitivity, or both), ketone bodies are used by some maternal tissues (e.g., skeletal muscle) as alternative substrates. Ketone bodies can also cross the placental barrier and be used as fuels and lipogenic substrates by the fetus.[165–170]

Maternal ketonemia in the poorly controlled pregnant diabetic patient, with or without acidosis, has been associated with an increased stillbirth rate, an increased incidence of congenital malformations, and impaired neurophysiologic development in the infant.[164, 169, 171, 172] These effects are thought to be secondary to placental transfer of maternal ketone bodies to the fetus.[173]

In addition to size and lipid solubility, molecular charge has an important effect on placental membrane permeability. At pH 7.4, most of the molecules of the two main ketone bodies, β-hydroxybutyrate and acetoacetate, are present in dissociated or ionized form, retarding their diffusion across the placenta. Despite this, in all species studied (human,[152, 160, 161, 174, 175] rat,[76, 77, 176] and sheep[159, 173]), increments in maternal ketone bodies are accompanied by increments in fetal plasma levels, indicating efficient placental transfer; fetal liver ketogenesis is practically negligible.[177]

Placental transfer of ketone bodies occurs by simple diffusion and has a high nonspecific component;[149] however, its efficiency varies among species. Although the maternofetal gradient for ketone bodies is above 10 in sheep,[159, 173] in humans it is about 2,[152] and in rats it is close to 1[76, 78, 176] (see Fig. 45–5), indicating that the amount of ketone bodies crossing the placenta is much lower in ruminant than in nonruminant species. It has even been proposed that in the fasting condition, the contribution of ketone bodies to the fetal oxidative metabolism accounts for only 2 to 3% of the total oxygen consumption in the case of sheep.[159, 178] In the rat, β-hydroxybutyrate adequately replaces the glucose deficit in the placenta, fetal brain, and liver during fasting hypoglycemia.[168] This suggests a much greater contribution of ketone bodies to the fetal oxidative metabolism in the fasted nonruminant.

Key enzymes for ketone-body utilization—3-hydroxybutyrate dehydrogenase (EC 1.1.1.30), 3-oxoacid-CoA transferase (EC 2.8.3.5), and acetyl-CoA acetyltransferase (EC 2.3.1.9)—have been found in the brain and other tissues in both the human and the rat fetus.[165, 167, 179–181] Both the human[69] and the rat brain[166] oxidize β-hydroxybutyrate *in vitro* in a form that is dependent on substrate concentration and not on the maternal nutritional state. Other fetal tissues known to oxidize ketone bodies are kidney, heart, liver, and placenta.[167, 181] Some tissues are even known to use ketone bodies as substrates for fatty acid and cholesterol synthesis, as has been shown in the rat brain, liver, placenta, and lung after *in vivo* administration of ^{14}C-β-hydroxybutyrate to pregnant animals.[182] The activity of ketone-body metabolizing enzymes in fetal tissues (brain, liver, and kidney) can be increased by conditions that result in maternal hyperketonemia, such as starvation during the last days of gestation[183] or high fat feeding.[180] Such a change is especially evident in the fetal brains from starved late pregnant rats[183] and may represent an important fetal adaptation to guarantee brain development under these conditions because fetal brain weight is better preserved than other fetal organ weights.[183]

In conclusion, there is evidence in nonruminant species for efficient placental ketone body transfer and for the fetal utilization of these materials as substrates for both oxidation and lipogenesis even in preference to other substrates (glucose, lactate, and amino acids). Because both the placental transfer and the utilization of ketone bodies are concentration dependent, the quantitative contribution to the fetal metabolism is important only under conditions of maternal hyperketonemia (e.g., starvation, high-fat diet, diabetes).

SUMMARY

During gestation, both triglyceride and cholesterol increase in all the lipoprotein fractions and are associated with an increase in the triglyceride/cholesterol ratio in LDL and HDL. The increase in HDL mainly corresponds to triglyceride-enriched HDL_2 and seems to be a consequence of de-

creased insulin sensitivity and increased circulating estrogen levels that are normally present during late gestation.

The placenta is an active lipoprotein-metabolizing organ, in which cholesterol and fatty acids from maternal lipoproteins are used for steroid hormone synthesis and transfer to the fetus.

Sustained maternal hyperlipidemia during late pregnancy is of pivotal importance in fetal development. This is especially true during the stage of maximal fetal accretion. Besides using transferred fatty acids (mainly derived from maternal FFA), the fetus also benefits from two other products of maternal lipid metabolism, glycerol and ketone bodies. The contribution of maternal cholesterol to fetal cholesterol seems, however, to be of minimal quantitative importance, and this is consistent with the high capacity of all fetal tissues to synthesize cholesterol.

Although maternally derived glycerol crosses the placenta in a small proportion, it is quantitatively important as a substrate for maternal gluconeogenesis. Because fetal oxidative metabolism is preferentially sustained by maternal glucose crossing the placenta, the use of glycerol for glucose synthesis actively contributes to the fetal glucose supply.

In nonruminant species, there is an easy transfer of maternal ketone bodies to the fetus, where they can be efficiently used as carbon fuels for oxidative metabolism or as lipogenic substrates. Because all these processes are concentration dependent, they become relevant only under conditions of maternal hyperketonemia. Under healthy physiologic conditions, they constitute an important support for fetal metabolism when the availability of other substrates is more limited (e.g., during periods of maternal starvation). Under conditions of sustained maternal hyperketonemia, such as high-fat feeding, fetal metabolism also adapts to an enhanced consumption of ketone bodies. There are conditions, however, such as poorly controlled diabetes, in which sustained maternal hyperketonemia seems to have deleterious effects on the fetus. The mechanism behind these effects remains to be established.

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