SECTION VI

Lipid Metabolism

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Maternal-Fetal Transfer of Lipid Metabolites

Changes in maternal lipid metabolism during gestation control the availability of lipid metabolites to the fetus, even though some components do not directly cross the placental barrier. This is the case of maternal plasma lipoproteins, the profile of which during pregnancy differs markedly from that seen in nonpregnant subjects. Although no evidence exists for their transfer to the fetus, placental cells have lipoprotein receptors that allow the uptake and release of their lipid components 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 and become 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.

HYPERLIPOPROTEINEMIA IN PREGNANCY AND ITS ROLE AS A SOURCE OF FATTY ACIDS FOR THE FETUS

Maternal hypertriglyceridemia is one of the most striking changes that takes place in lipid metabolism during gestation. The increase in plasma triglycerides during pregnancy is greater than increases in phospholipids and cholesterol,[1,2] and more triglycerides are found in all the lipoprotein fractions.[3-6] As shown in Figure 39-1, although both triglycerides and cholesterol in very low density lipoproteins (VLDLs), low density lipoproteins (LDLs), and high density lipoproteins (HDLs) are higher in pregnant women in the third trimester of gestation than in the same women during postlactation, the triglyceride/cholesterol ratio remains stable in VLDL despite significant increases in both LDL and 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 in the maternal lipoprotein profile during pregnancy are summarized in Figure 39-2. The increased adipose tissue lipolytic activity during late gestation[8-10] (which is mediated by an insulin-resistant condition[11]) enhances the availability of substrates for triglyceride synthesis in the liver. This action, together with the stimulating effect of estrogen on VLDL production[12] and the decreased extrahepatic lipoprotein lipase (LPL) activity,[7,13,14] 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, as seen in the rat, this is the body tissue that normally has the highest LPL activity and is the only tissue that shows an intense decrease during late gestation.[15-19] The decreased adipose tissue LPL activity is also a consequence of the insulin-resistant state present during late pregnancy.[11,20] Although the abundance of VLDL could justify an enhanced conversion to lipoproteins of higher density, the specific enrichment in triglycerides 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),[7,21] 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,[7,13] 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 and mRNA expression.[13,22-24]

The events just summarized 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 reduction of maternal hyperlipoproteinemia in animals by treatment with hypolipidemic drugs has negative effects on fetal development.[25,26]

Essential fatty acids (EFAs) derived from maternal diet, which are transported in maternal plasma as triglycerides in triglyceride-rich lipoproteins, must become available to the fetus, despite the lack of a direct placental transfer of maternal lipoproteins. This transfer occurs thanks to the presence of lipoprotein receptors in the placental trophoblast cells that lie at the interface with maternal blood. These cells are therefore positioned to bind maternal lipoproteins and mediate their metabolism and subsequent transfer of the EFAs they deliver to the fetal circulation. VLDL/apo E receptor (VLDLR) as well as LDL receptor (LDLR) and LDLR-related proteins are expressed in human placental tissue.[27-36]

Placental tissue expresses lipoprotein lipase (LPL) activity[37-42] as well as phospholipase A_2[43,44] and intracellular lipase activities.[45-47] Maternal triglycerides in plasma lipoproteins are therefore hydrolyzed and taken up by the placenta, where their re-esterification and intracellular hydrolysis facilitate the diffusion of released fatty acids (FAs) to the fetus and their subsequent transport to fetal liver. In fact, by using cultured placental trophoblast cells, it has been shown that esterified cellular lipids provide a reservoir of FAs that can be released into the medium.[48]

Once released into fetal plasma, placental transferred FAs bind to a specific oncofetal protein, the α-fetoprotein[49-51] and are rapidly transported to fetal liver. Those FAs taken up by fetal liver

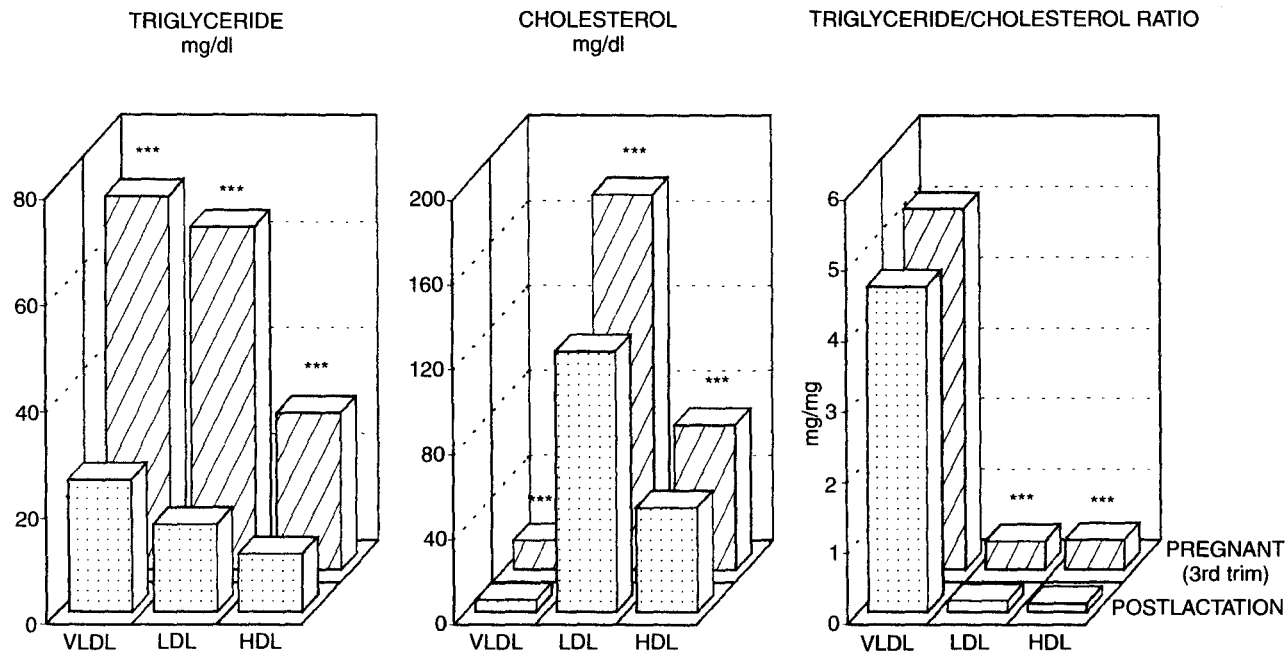

Figure 39–1. Plasma lipoprotein lipids in women in the third trimester of pregnancy and at postlactation. Asterisks indicate significant differences between the two groups.

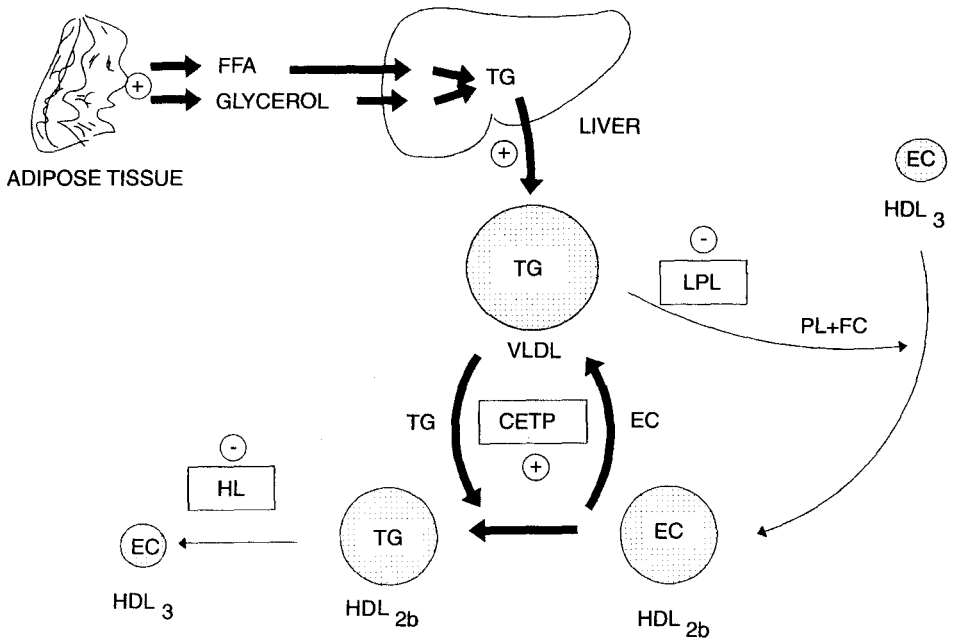

Figure 39–2. Proposed control of major pathways of very low density lipoprotein (VLDL) and high density lipoprotein (HDL) metabolism during late pregnancy. FFA = free fatty acids; LPL = lipoprotein lipase; HL = hepatic lipase; CETP = cholesteryl ester transfer protein; LCAT = lecithin cholesterol acyl transferase; TG = triglycerides; EC = esterified cholesterol; FC = free cholesterol; PL = phospholipids.

are esterified and released back into circulation in the form of triglycerides. This is consistent with the significant linear correlation found for certain long chain polyunsaturated fatty acids (LCPUFAs) between maternal plasma and cord plasma triglycerides during late gestation in humans.[52] A linear correlation has also been found between maternal and fetal plasma triglycerides in the rat.[14,53] This relationship may have important implications in newborn weight, because a direct relationship between maternal triglycerides and newborn weight has been found in humans.[54-56]

MATERNAL LIPID METABOLISM AND PLACENTAL TRANSFER OF FREE FATTY ACIDS, GLYCEROL, AND KETONE BODIES TO THE FETUS

During the first part of gestation, the maternal body accumulates fat[57-59] as the result of combined effects of hyperphagia,[60,61] enhanced lipogenesis,[62] and unmodified or even increased extrahepatic LPL activity.[63] The tendency to accumulate fat ceases during late gestation[57,58,64,65] because maternal lipid metabolism changes to a catabolic condition. This is evidenced by increased

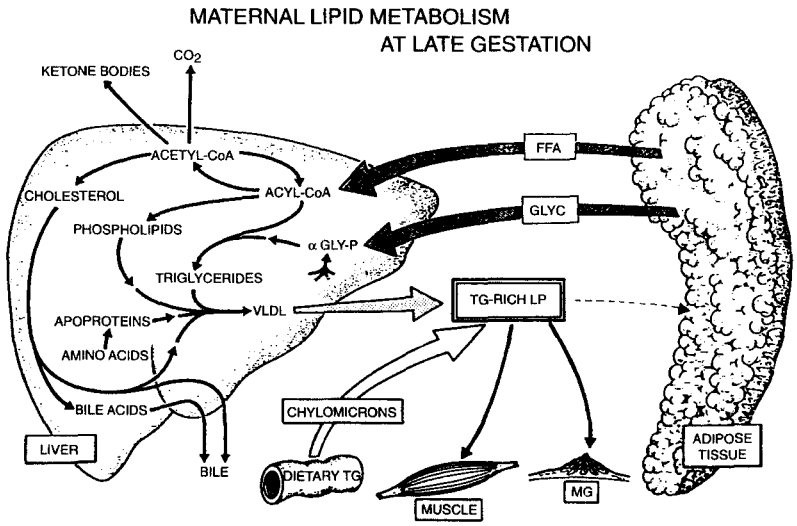

Figure 39–3. Summary of major changes in maternal lipid metabolism at late gestation. FFA = free fatty acids; TG-RICH LP = triglyceride-rich lipoproteins; Glyc = glycerol. (Adapted from Herrera E, et al: Biol Neonate *51*:70–77, 1987. S. Karger AG, Basel.)

adipose tissue lipolysis[9,17,66] and reduced uptake of circulating triglycerides,[67] secondary to the reduction in adipose tissue LPL activity,[7,13–15,18,19] reviewed earlier in this chapter. These changes, together with hepatic overproduction of triglycerides[68,69] and the enhanced absorption of dietary lipids,[70] are responsible for the marked progressive increase in maternal circulating triglycerides occurring during late gestation.[3,4,71,72] The major changes in the maternal lipid metabolism are summarized in Figure 39–3, 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 no different from that in nonpregnant subjects, but it increases markedly under fasting conditions.[73,74]

With the exception of glycerol used in gluconeogenesis[75,76] and the LPL-mediated circulating triglyceride uptake by the mammary gland before labor,[18,70,77,78] 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 this may explain the well-known finding of enhanced ketogenesis in the mother under fasting conditions.[73,79–81] This hypothesis is supported by data demonstrating an increased arrival of FFA in the liver as a result of the greatly enhanced adipose tissue lipolysis[8,9,66] and by studies reporting an increase in liver LPL activity,[16,82,83] which facilitates maternal liver use of circulating triglycerides as ketogenic substrates.

The enhanced availability of ketone bodies to fasted maternal tissues allows them 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. 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.[16,75] Glycerol can be used as an efficient gluconeogenic substrate[75,76,84,85] and therefore contributes to the maintenance of glucose production for fetal and maternal tissues. Metabolic adaptations found in the mother during starvation are summarized in Figure 39–4. 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.

Understanding FAs, 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 39–5 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.

Maternal/fetal nutrient transfer through the placenta may be accomplished by means of different mechanisms, including facilitated diffusion, active transport, and simple diffusion.[86–88] The rate of transfer by simple diffusion seems to be a common mechanism for FAs and related moieties. It is a direct function of the concentration gradient and decreases with the molecular size and hydrosolubility.[89] However, in the case of placental transfer, other factors also participate:[90,91] uterine and umbilical blood flows, intrinsic placental metabolism, and structural characteristics. As may be expected, some of these factors, such as blood flow, contribute analogously to the transfer of any nutrient, but other factors differ with each nutrient and require specific consideration.

Fatty Acids

The fetus requires not only essential FAs 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 pigs and 16% in humans),[95] and *de novo* FA synthesis by fetal tissues cannot fulfill fetal requirements.

Either FFA bound to albumin or esterified FAs transported in lipoproteins are the potential sources of the FAs in the maternal side that cross to the placenta. Early studies in 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 FFAs did not appear to constitute a significant part of the metabolic fuel supplied there by the mother.[96] Later

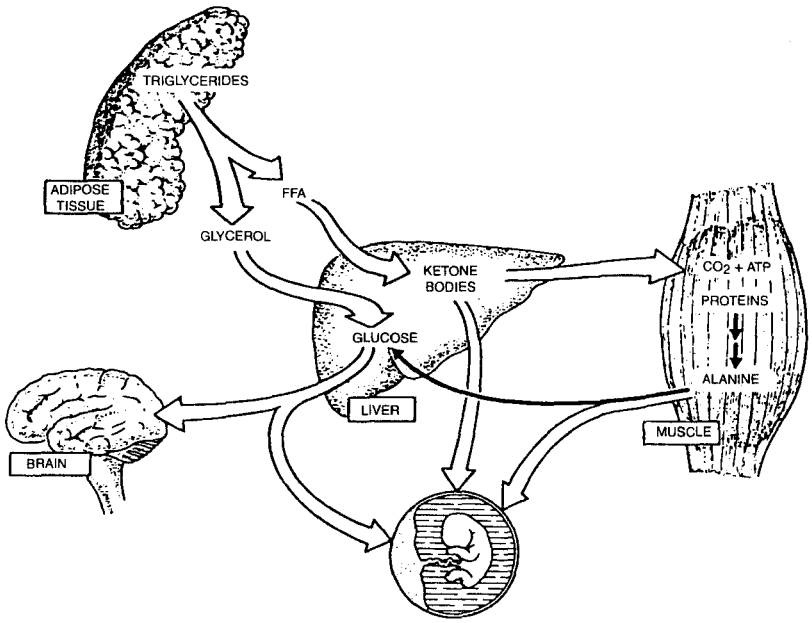

Figure 39–4. Maternal response to starvation. Enhanced adipose tissue lipolysis increases the availability in the liver of glycerol to be used as a preferential substrate for gluconeogenesis and of free fatty acids (FFAs) for ketone body synthesis. By this mechanism, the mother conserves other gluconeogenic substrates, such as alanine, and ensures the adequate availability of fuels and metabolites to the fetus. ATP = adenosine triphosphate (From Herrera E, et al: Biol Neonate *51*: 70–77, 1987. S. Karger AG, Basel.)

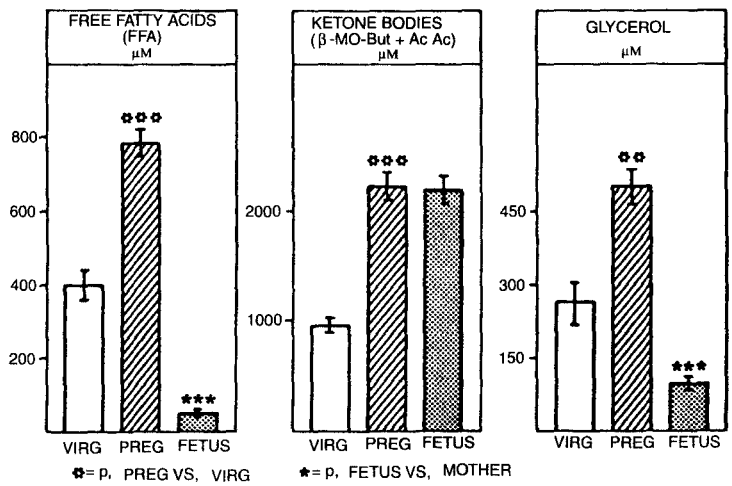

Figure 39–5. Concentration of free fatty acids, ketone bodies, and glycerol in plasma of 48-hour starved virgin rats and 48-hour starved 19-day pregnant rats and thier fetuses. (From Herrera E, et al: Biol Neonate *51*: 70–77, 1987. S. Karger AG, Basel.)

studies demonstrated, however, that the net flux of FAs 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 FA 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 FAs crossing the placenta exceeds even that needed to fulfill lipid storage requirements.[107] In these species, the FA mixture entering fetal circulation from the placenta reflects the maternal FFA concentrations of the different FAs.[97] Furthermore, maternal dietary manipulation with different oil-enriched diets leads to corresponding changes in the FA composition of the fetus.[108,109] These observations, therefore, constitute indirect evidence for the transplacental passage of FAs from mother to fetus.

In humans, although in a smaller proportion than lipoprotein triglycerides, maternal plasma FFAs are an important source of polyunsaturated FAs (PUFA) to the fetus.[110,111] Current evidence suggests that cellular uptake of FFA occurs through a process of facilitated membrane translocation involving a plasma membrane FA-binding protein ($FABP_{pm}$).[112,113] It has been shown that $FABP_{pm}$ is present in human placental membranes[114,115] and is responsible for the preferential uptake of LCPUFAs by the human placenta.[114,116] The preference for human placental transfer from the maternal to the fetal circulation has been reported as docosahexaenoic⇒ α-linolenic⇒ linoleic⇒ oleic⇒ arachidonic acid.[117] Arachidonic acid was, however, the FA with the highest accumulations in the placenta,[117] and more recently it has been shown that this process of arachidonic uptake by placental syncytiotrophoblast membranes is highly dependent on adenosine triphosphate (ATP) and sodium,[118] implying an active transport mechanism for this FA. A selectivity in the LCPUFA placental transfer may also be exerted at the level of cellular metabolism, given that a certain proportion of arachidonic acid is converted to prostaglandins,[111] a selective incorporation of certain FAs into phospholipids has been found in the ovine placenta,[119] and even selective placental FA oxidation[120,121] and lipid synthesis[122,123] may occur.

The combination of all these processes determines the actual rate of placental FA transfer and its selectivity. Through these mechanisms, the placenta selectively transports arachidonic acid and docosahexaenoic acid from the maternal to the fetal compartment, resulting in a proportional enrichment of these LCPUFAs in circulating lipids in the fetus.[124] This occurs during the third trimester, when the fetal demands for neural and vascular growth are greater.[125-127]

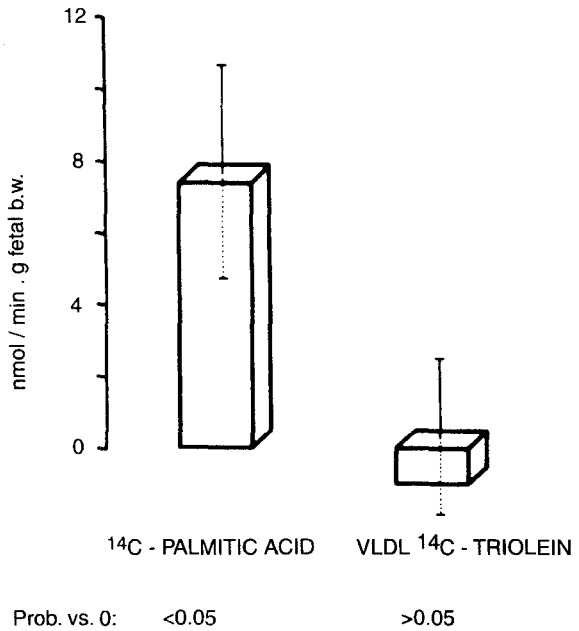

Figure 39–6. Estimation of placental transfer of palmitic acid and VLDL-triolein in the 20-day pregnant rat. Placental transfer to the fetus was determined by measuring the radioactivity appearing in fetuses after infusing ^{14}C-labeled substrates through the left uterine artery and making proper correction of the data for specific activity dilution of the tracer and uterine blood flow, as previously described (see ref. 137).

Although, as commented on earlier, current evidence indicates that FAs are selectively transferred across the placenta, essential and nonessential FAs may also 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.[128-130] Furthermore, during maternal fasting, increased amounts of maternal FFA cross the placenta into fetal circulation and are incorporated into fetal stores.[131] These observations suggest that the transfer of several FFA across the placenta is mainly by diffusion. Other factors affecting this transfer process are the uterine and umbilical blood flow rates[128,130] and the fetal plasma albumin concentration.[128,132,133] In this respect, the increase in albumin levels throughout the third trimester in the human fetus[134] may increase its FFA supply.

The authors have studied the placental transfer of palmitic acid 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.[135] Although the left uterine horn received the tracer directly, it reached the right horn after dilution in the mother's circulation. Therefore, the amount of substrate transferred to the fetus can be calculated as a function of the values for the concentration of the metabolite studied in maternal plasma, the difference of radioactivity in fetuses between the left and right uterine horns, and the left uterine blood flow.[136-139] As shown in Figure 39-6, the estimated FFA transfer was above 7 nmol/min × g fetal body weight, a value that is lower than the level previously found for other compounds in earlier studies: glucose, 127 nmol/min × g fetal body weight; alanine, 23 nmol/min × g fetal body weight, but higher than that of glycerol, 1 nmol/min × g fetal body weight.[139] 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 value was 99 ± 38 nmol/min/g, 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 FAs, indicating that a certain proportion of the FFA that reach the placenta is actively esterified. It is not known whether FA esterification participates in the FFA transfer process, but an active placental capacity to form esterified FAs from maternal FFA has also been described in other species[140,141] as well as in humans.[48,142]

As already noted, maternal plasma triglycerides in triglyceride-rich lipoproteins may be considered as an alternative source of FAs for the fetus. We have recently found that the concentration of PUFA in plasma VLDLs in pregnant women during the third trimester of pregnancy is much greater than that in FFA[53] and previous evidence indicates that maternal circulating triglycerides contribute somewhat to plasma fetal FAs of the rat,[143] rabbit,[39] guinea pig,[41,144] and human.[145] The authors applied the *in situ* uterine artery infusion technique[135] described above to test the potential transfer of VLDL-^{14}C-triolein across the placenta and its incorporation into fetal lipids. 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 (see Fig. 39-6). Therefore, it was concluded that lipoprotein triglycerides are not a significant direct FA source for placental transfer to the fetus.

Glycerol

As a result of the active lipolytic activity of maternal adipose tissue, plasmatic glycerol levels are consistently elevated during late gestation.[17,75,76] Therefore, the values for plasma glycerol are generally higher in the mother than in the fetus (see Fig. 39-5), but there are some interspecies differences. The maternal/fetal glycerol gradient is greater in those species with an epitheliochorial placenta (ruminants)[96,146] than in those with a hemochorial placenta.[147-149]

The available experimental data on placental glycerol transfer in any species are scarce. Although the molecular characteristics of glycerol should facilitate 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.[139,150,151] In contrast with the carrier-mediated process used for these two metabolites, placental glycerol transfer is accomplished by simple diffusion.[146,152] In the sheep fetus, glycerol 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.[147] 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.[139] The authors have also found that the fetal-placental unit converts glycerol into lactate and lipids,[149] and this rapid use may actively contribute to maintaining the high glycerol gradient consistently found between maternal and fetal blood.[81,147-150]

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.[75,76,84,85] Although this mechanism indirectly benefits the fetus by providing glucose (see Fig. 39-4), it may limit the availability of sufficient glycerol molecules for transfer to the fetus. Figure 39-7 summarizes studies that support this hypothesis. Hepatectomy normally results in increased plasma glycerol levels because of a reduction in glycerol use secondary to absence of the liver, the major receptor organ for this metabolite.[153] In the case of pregnant rats, hepatectomy and nephrectomy produce significant but smaller increases in plasma glycerol levels than in nonpregnant animals. This difference cannot be

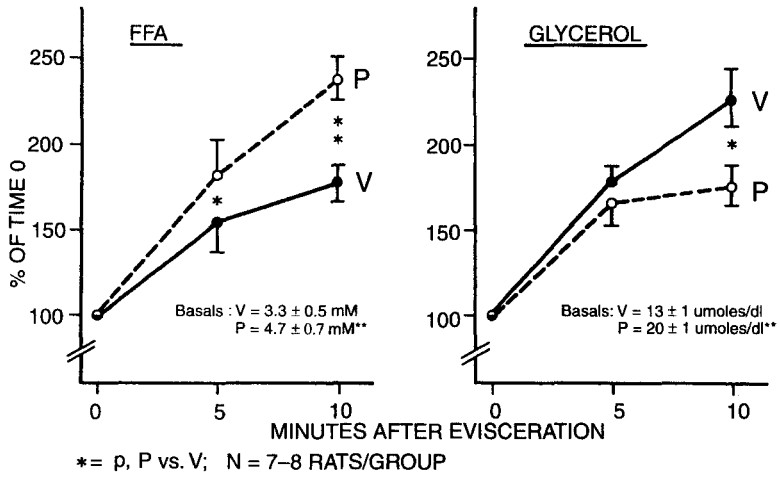

Figure 39–7. Effect of hepatectomy-nephrectomy on plasma free fatty acid and glycerol in virgin (V) and 20-day pregnant rats (P). Experimental details are as indicated in ref. 154.

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.[154]

Therefore, placental glycerol transfer seems to be limited by the effective, rapid use of this substrate for gluconeogenesis 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 roles in the fetus, except as a preferential substrate for fetal liver glyceride glycerol synthesis,[149] seem 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; with fasting[73, 79, 80, 155-159] or diabetic[3, 160, 161] 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.[162-165]

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, 166, 167] These effects are thought to be secondary to placental transfer of maternal ketone bodies to the fetus.[168]

In addition to size and lipid solubility, molecular charge has an important effect on placental membrane permeability. At pH 7.4, most molecules of the two main ketone bodies, β-hydroxybutyrate and acetoacetate, are present in dissociated or ionized form, which retards their diffusion across the placenta. Despite this, in all species studied (human,[157, 158, 169, 170] rat,[79, 80, 171] and sheep[156, 168]), increments in maternal ketone bodies are accompanied by increments in fetal plasma levels, indicating efficient placental transfer; fetal liver ketogenesis is practically negligible.[172]

Placental transfer of ketone bodies occurs either by simple diffusion or by a low specificity carrier-mediated process;[146, 173] the efficiency of which varies among species. Although the maternofetal gradient for ketone bodies is higher than 10 in sheep,[156, 168] in humans it is about 2,[147] and in rats it is close to 1[79, 80, 171] (see Fig. 39-5), indicating that the amount of ketone bodies crossing the placenta is much lower in ruminants 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.[156, 174] In the rat, β-hydroxybutyrate adequately replaces the glucose deficit in the placenta, fetal brain, and liver during fasting hypoglycemia.[165] 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.[162, 163, 175, 176] Both the human[164] and the rat brain[163] oxidize β-hydroxybutyrate *in vitro* in a form that is dependent on substrate concentration and not on the maternal nutritional state. Other fetal tissue types known to oxidize ketone bodies are kidney, heart, liver, and placenta.[163, 176] Some tissues are even known to use ketone bodies as substrates for FA 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.[177] 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[178] or high fat feeding.[179] Such a change is especially evident in the fetal brains from starved late pregnant rats[178] 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.

In conclusion, there is evidence in nonruminant species for efficient placental ketone body transfer and for the fetal use 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 use of ketone bodies are concentration dependent, the quantitative contribution to fetal metabolism is important only under conditions of maternal hyperketonemia (e.g., starvation, high-fat diet, diabetes).

CHOLESTEROL IN THE FETUS

Role of Cholesterol and Related Compounds in Development

Cholesterol plays an important role in fetal development as well as in the general physiology of the organism. First, it is an essen-

tial component of cell membranes. By interacting with phospholipids and sphingolipids, cholesterol contributes to the characteristic physicochemical properties of membranes, mainly fluidity and passive permeability.[180] Cholesterol is not homogeneously distributed in the membrane, rather it is concentrated in structures such as rafts and caveolae, where it modulates the function of different integral proteins and receptors. Cholesterol is the precursor of both bile acids and steroid hormones; in the fetus, glucocorticoids are intensely synthesized by the adrenal gland in the last part of development, which represents an important time of cholesterol need. Cholesterol and its oxidized derivatives—oxysterols—are key regulators of different metabolic processes, both by modulating the proteolytic activation of sterol response element binding protein (SREBP) or by acting as ligands of nuclear receptors, such as LXR (liver X receptor).[181,182] Active SREBP and LXR are transcription factors that regulate the expression of multiple genes implicated in intracellular lipid homeostasis and lipoprotein metabolism.[181,183]

Recently, other important actions of cholesterol have become apparent; these actions have special relevance for the fetus because they are related to development, embryogenesis, and differentiation. Cholesterol is required for cell proliferation, not only for membrane formation, but also for the activation of regulatory proteins involved in cell cycle progression, specifically in the transition from the G2 phase to mitosis.[184,185] Cholesterol plays important roles in differentiation and cell-to-cell communication; in fact, it has recently been demonstrated as a key factor in synaptogenesis.[186] Finally, cholesterol is essential in embryonic patterning in both vertebrates and invertebrates.[187] This is attained mainly by activation of hedgehog proteins (i.e., Sonic hedgehog—Shh—in humans), which are involved in cell differentiation.[188]

It is conceivable, thus, that defects affecting cholesterol availability will have deleterious consequences in fetal development. In fact, congenital defects in cholesterol biosynthesis or the reduction of cholesterol synthesis with xenobiotics result in severe malformations and dysfunctions, mainly affecting the craniofacial organs and the central nervous system (CNS), respectively, alterations that are similar to those caused by Shh defficiency.[187,189,190]

It has been observed in pigs that fetal weight is directly correlated to plasma cholesterol concentration in the fetus at late gestation.[191] Similarly, neonatal pigs from lines with genetically low cholesterol levels are smaller at birth and grow more slowly, but the growth rate improved when they were fed with cholesterol.[192,193] An increase in neonatal survival is noted with supplementary dietary fat for the peripartal sow.[194] Thus, cholesterol is essential in body growth and the development of the CNS and fetal requirements must be met either by efficient endogenous cholesterol biosynthesis or transfer from the mother.

Cholesterol Biosynthesis and Congenital Defects

Cholesterol biosynthesis is a multienzymatic pathway that can be separated into three segments according to the type of compounds that are synthesized in each one, that is, mevalonic acid, isoprenoids, and sterols, respectively. In the first, also called the *mevalonate pathway*, three molecules of acetyl-CoA are successively condensed by the action of acetyl-CoA acetyltransferase and cytosolic 3-hydroxy-3-methylglutaryl (HMG)-CoA synthase to form HMG-CoA, which is then reduced with the loss of coenzyme A, rendering mevalonate, a 6-carbon compound[195] (Fig. 39-8). This complex reaction is catalyzed by HMG-CoA reductase, which is present in the endoplasmic reticulum and is the rate-limiting step in cholesterol biosynthesis. In the next series of reactions, mevalonate is converted to squalene (see Fig. 39-8), which is the immediate precursor of sterols. The first sterol formed is lanosterol, which contains 30 carbons (see Fig. 39-8). The transformation of lanosterol into cholesterol occurs in the endoplasmic reticulum and involves at least seven different enzymes (Fig. 39-9).

In humans, six different genetic defects in the cholesterol biosynthesis pathway have been identified. Mevalonic aciduria (MIM 251770) is caused by missense mutations in mevalonate kinase, which impair the formation of both isoprenoids and sterols (see Fig. 39-8). The patients show dysmorphias and failure to thrive. Milder mutations of the enzyme also underlie hyperimmunoglobulinemia D and periodic fever syndrome (MIM 260920). The rest of the disorders are due to defects in the post-squalene segment of the pathway (see Fig. 39-9). Greenberg skeletal dysplasia (MIM 215140), which is associated with short-limb dwarfism, is probably caused by mutations of Δ^{14}-reductase, but confirmation at the molecular level has yet to be observed. CHILD syndrome (MIM 308050) and Conradi-Hünermann-Happle syndrome (CPDX2; MIM 302960) are caused by deficiencies of C4-demethylase and Δ^{8}-Δ^{7}-isomerase, respectively; these two disorders are X-linked dominant inherited and carrier males are lethally affected, whereas females present with several skeletal and skin abnormalities. Desmosterolosis (MIM 602398) is an extremely rare and probably autosomal recessive inherited disorder due to the deficiency of Δ^{24}-reductase; the infants affected died shortly after birth and suffered from multiple malformations and dysmorphias. The last of these disorders, and probably the best known and most widely studied, is Smith-Lemli-Opitz syndrome (SLOS; MIM 270400), which is caused by mutations of Δ^{7}-reductase. The phenotypic expression is highly variable; the most prominent anomalies are microcephalia and facial dysmorphias. All affected patients accumulate 7-dehydrocholesterol in plasma and tissues, but the clinical severity of this syndrome correlates best with its relative level to plasma cholesterol. This suggests that the availability of cholesterol during development is one of the major determinants of the phenotypic expressions in SLOS.

In general, these congenital alterations show the important role of cholesterol and its immediate precursors in morphogenesis and fetal development. The reader is referred to excellent reviews on this subject.[189,190]

Sources of Fetal Cholesterol

The demands for cholesterol in the fetus are relatively high, especially during the last third of gestation when fetal growth is exponential. In principle, the fetus may obtain cholesterol from both endogenous biosynthesis and from the yolk sac and placenta. By following the appearance of radioactivity in the fetus, early experiments demonstrated the placental transfer of maternal cholesterol to the fetus in different species, such as the rat,[196] guinea pig, rabbit,[197] and rhesus monkey.[198] In those studies, the estimated contribution of maternal cholesterol to the fetus varied widely, likely because of methodologic reasons. A more accurate type of study is to compare cholesterol accretion in the fetus with the absolute rate of cholesterol biosynthesis. Measurements of [^{3}H]water incorporation into cholesterol revealed that cholesterol biosynthesis in fetal tissues is highly active; when calculated per mass unit, the rate of cholesterol synthesis in fetal tissues is several times higher than in maternal tissues in different species.[199-203] This is especially the case for the fetal brain, which appears almost completely autonomous in cholesterol accretion, and the liver, the cholesterol biosynthesis of which proceeds at a rate exceeding the need for cholesterol accretion, an excess that is secreted into the plasma for uptake by other developing fetal organs.[202,203] These results are consistent with the near-maximal expression at the level of mRNA of different enzymes involved in cholesterol biosynthesis[204] and the high activity of HMG-CoA reductase—the rate limiting enzyme of cholesterol biosynthesis—in fetal tissues.[205,206]

By comparing the cholesterol synthesis rate with cholesterol accretion in the whole fetus, an estimation of the requirement for exogenous cholesterol can be derived, which would either be directly transferred from maternal plasma or synthesized in the placenta or the yolk sac. In the rat, endogenously synthesized

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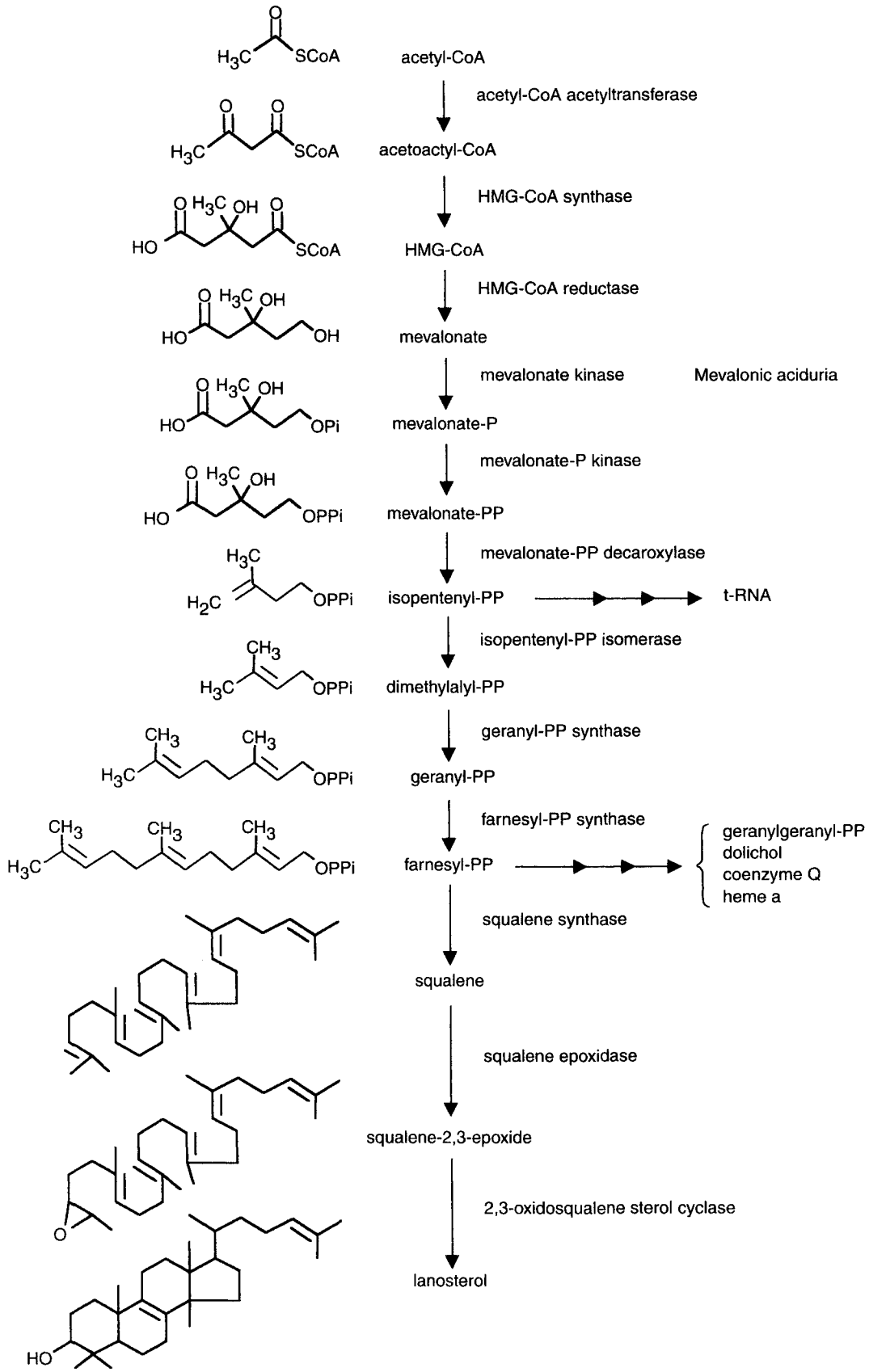

Figure 39–8. Biosynthesis of lanosterol from acetyl-CoA. Aside the route leading to the formation of lanosterol, the first sterol in the cholesterol biosynthesis pathway, the alternative use of isopentenyl-PP for the derivation of certain t-RNA and farnesyl-PP for several isoprenoids is shown. Multiple arrows indicate several reactions. The name of a human inherited disorder is shown in italics beside the affected enzyme.

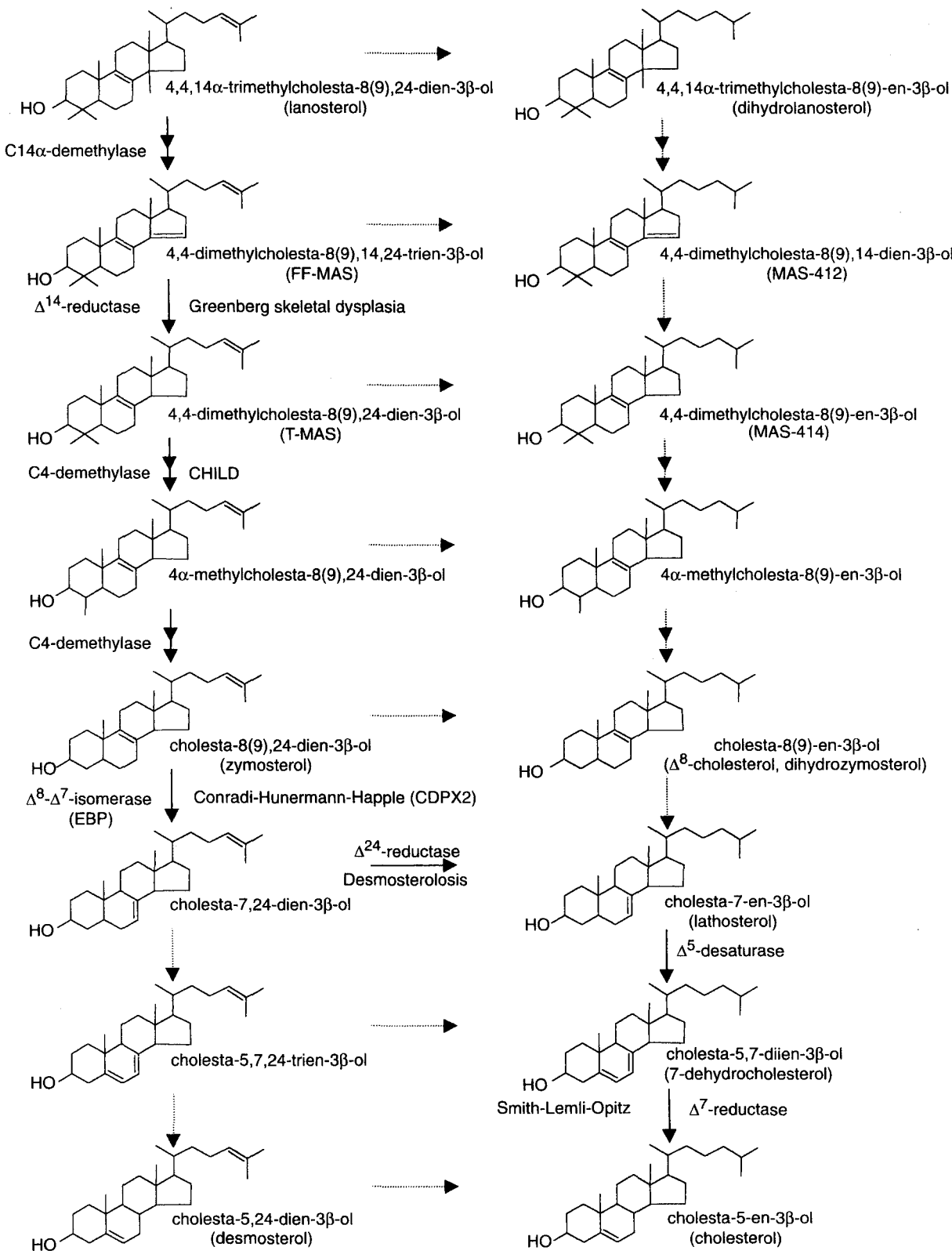

Figure 39–9. Biosynthesis of cholesterol from lanosterol. The main route is indicated by the solid arrows (see text for comments). Double arrows indicate several reactions. The names of the human inherited disorders are shown in italics beside the affected enzymes.

cholesterol appears to account for practically all fetal cholesterol,[202, 203] meaning that the other potential sources are insignificant, at least during the later stages of gestation. In fact, Belknap and Dietschy[200] found that although the rat placenta did take up ^{125}I-cellobiose-labeled lipoprotein from maternal circulation, none of the apolipoprotein or cholesterol was appreciably transferred to the fetus. These studies indicate that the rat fetus receives little or no cholesterol from the mother but, rather, satisfies its need for cholesterol during fetal development through local synthesis. Maneuvers directed to modify cholesterol homeostasis in the mother had no significant effects on cholesterol levels or cholesterol synthesis rates in the fetus. Thus, feeding pregnant rats with cholesterol, which resulted in an increase of plasma cholesterol concentration and reduced cholesterol synthesis in the maternal compartment, did not affect any of these parameters in the fetus.[199,200,207,208] Conversely, treatment of pregnant rats with cholestyramine—a bile acid sequestrant that interferes with intestinal cholesterol absorption and consequently stimulates cholesterol biosynthesis in maternal tissues—did not alter cholesterol accretion in the fetus.[209] All these findings led to the affirmation that in the rat, fetal cholesterol originates mainly from endogenous *de novo* synthesis rather than from placental transfer.

In the early stages of gestation in the rat, however, maternal cholesterol may make a significant contribution to the fetal cholesterol pool. For instance, it is well known that treatment of pregnant rats with AY 9944—an inhibitor of Δ^7-reductase—results in fetal teratogenesis, but the simultaneous oral administration of cholesterol early in gestation completely prevents the characteristic holoprosencephalic brain malformations.[187,210,211] In contrast, the anomalies of fetal masculinization caused by AY 9944 when administered late in gestation, are not prevented by the compensatory administration of cholesterol to the mother.[187] These results firmly suggest that maternal cholesterol reaches the fetal compartment at least early in gestation and is of significant physiologic relevance in the rat.

In other species, exogenous cholesterol may constitute an important, quantitative source of cholesterol for the fetus. In the Golden Syrian hamster, Woollett found that endogenous biosynthesis accounted for only 40% of the fetal cholesterol, suggesting that the placenta and/or the yolk sac contributed the remainder.[201] Actually, in hamsters fed increasing amounts of cholesterol, the cholesterol concentration in the fetal tissues was found to be linearly correlated with the maternal plasma cholesterol concentration, while cholesterol synthesis decreased in the reverse way.[212] These studies in hamsters demonstrated that fetal cholesterol homeostasis is affected by maternal plasma cholesterol concentration in a gradient fashion.[212] In the guinea pig, fetal cholesterol homeostasis was found to be relatively insensitive to dietary cholesterol manipulations in the mother throughout gestation.[199] Nevertheless, feeding cholestyramine to the mothers, although producing the expected stimulation of ^{3}H-water incorporation into sterols in maternal liver, also resulted in a 1.4-fold increase in fetal carcass cholesterol synthesis at 60 days' gestation, which demonstrates that fetal cholesterol homeostasis may respond to induction by maternal hypocholesterolemia during the late gestation period.[199]

Data in humans are scarcer and cholesterol biosynthesis in fetal tissues has not been evaluated for obvious reasons. In deliveries at term, Parker and associates[213] measured cholesterol levels in the umbilical venous and the umbilical arterial plasmas and found a highly significant difference between HDL-, LDL-, and total-cholesterol concentrations, venous levels being 7.7 to 12.8% higher than those in arterial plasma. These data were suggestive of the delivery of cholesterol from the placenta to the fetus, which could either be synthesized in the placenta or derived from the maternal plasma. Those same authors, however, estimated that the contribution of such cholesterol to the fetal plasma cholesterol pool was of minimal quantitative importance in term newborns of women experiencing uncomplicated pregnancies.[213] Several observational studies have addressed this issue by comparing maternal lipoprotein-cholesterol levels with those in mixed umbilical cord blood, reporting either a positive correlation[214, 215] or no correlation between these values.[213,216-218] The gestational stage, however, could influence these results, because cholesterol plasma concentration has been reported as significantly higher in premature than in full-term newborns.[219, 220] In fact, fetal cholesterol levels show a strong inverse correlation with fetal age, being two-fold higher in 5-month than in 7-month-old fetuses.[221] This has been interpreted as an indication of the greater requirements of cholesterol in the younger, more immature fetuses.[221] Interestingly, in fetuses younger than 6 months, although not in older fetal plasma, cholesterol levels are significantly, directly correlated to the maternal ones.[221] Therefore, available results in humans strongly suggest that maternal cholesterol substantially contributes to fetal cholesterol accretion early in gestation.

Both the placenta and the yolk sac are able to synthesize and remove cholesterol from the maternal circulation. In the pregnant rat it was determined that placenta takes up LDL at rates equal to about one-third of those seen in the maternal liver.[200] In the hamster, LDL clearance rates of the placenta and yolk sac were similar to those in the liver and higher than those in the decidua when studied at mid-gestation (day 10.5).[222] In the same study, it was found that clearance rates for HDL-apoA-I and HDL-cholesteryl ether were similar to those of LDL in the placenta and decidua, whereas rates in the yolk sac were dramatically higher. As gestation progressed to day 14.5, LDL and HDL clearance rates decreased in all three tissues.[222]

Regarding the receptors responsible for the uptake of lipoprotein cholesterol, there are multiple possibilities. Both the placenta[223, 224] and, to a lesser extent, the yolk sac[222] express LDL receptors in their membranes. In correlation with this, several authors documented the use of LDL-cholesterol for progesterone synthesis by trophoblastic cells in vitro.[225,226] Interestingly, it was found that HDL_2-cholesterol stimulated placental progesterone secretion to a greater extent than LDL did, by a mechanism that did not involve the LDL receptor.[226] Further evidence on the role of maternal HDL as an exogenous source of fetal cholesterol comes from studies in apolipoprotein A-I-deficient mice. These animals have markedly reduced HDL-cholesterol levels in plasma, and cholesterol accretion in the fetus was diminished, although cholesterol synthesis in the fetus was not affected.[227] These results were in line with previous observations by Knopp and associates,[228] describing apolipoprotein A-I concentration in maternal plasma as a significant positive predictor of birth length. It appears that HDL could potentially contribute a significant proportion of the cholesterol required for fetal development.

Several lipoprotein receptors, different from the LDL receptor, which can mediate the uptake of HDL cholesterol, have been detected in placental preparations. These include SR-BI/CLA-1—an HDL receptor, megalin/gp330—homologue of the LDL receptor, and cubilin—a protein that binds HDL and acts in conjunction with megalin to mediate HDL endocytosis.[222,229,230] These receptors are highly expressed in the yolk sac as well.[222, 231, 232] Taken together, these data confirm the ability of both the placenta and the yolk sac to take up cholesterol from maternal lipoproteins, but the extent to which it is exported to the fetus and the factors that regulate this process remain to be clarified definitively.

SUMMARY

During gestation, both triglyceride and cholesterol increase in all 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. 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.

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 FAs, the fetus also benefits from two other products of maternal lipid metabolism, glycerol and ketone bodies. Although only a small proportion of maternally derived glycerol crosses the placenta, 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.

Although the contribution of maternal cholesterol to fetal cholesterol appears important during early gestation, it seems to be of minimal quantitative importance during late gestation. This is consistent with the high capacity of all fetal tissues to synthesize cholesterol. In humans, several congenital defects in the cholesterol biosynthesis pathway have been identified, showing the important role of cholesterol in morphogenesis and fetal development.

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