

Maternal Lipid Metabolism and Its Implications for Fetal Growth

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During gestation, the mother has to adapt her own metabolism to support a continuous extraction of nutrients through the placenta to sustain fetal development. Quantitatively, glucose and amino acids are the most abundant of these nutrients crossing the placenta (1,2), and the continuous dependence of the fetus on these compounds is well-known. However, the placenta is practically impermeable to lipids, except for free fatty acids (FFA) and ketone bodies (3). Nevertheless, the marked changes in the maternal lipid metabolism during gestation do have important implications for fetal growth. Two consistent manifestations of altered maternal lipid metabolism occurring during gestation are the accumulation of lipids in maternal tissues (4,5) and the development of maternal hyperlipidemia (6,7). It is known that conditions that restrain or alter any of these manifestations—such as hypothyroidism or overt diabetes during the first half of gestation—will greatly affect fetal growth at late gestation, even if they are compensated for by appropriate hormonal treatment during the second half of gestation (8,9).

In this chapter, we analyze the changes that occur in maternal lipid metabolism during gestation and how they contribute to fetal development.

MATERNAL ADIPOSE TISSUE METABOLISM

The increase in maternal body weight during gestation corresponds both to the growth of the fetal-placental unit and to the increase in the mother's own structures, which is mainly related to lipid accumulation in fat depots. A phenomenon common to humans (5,10) and rats (4,11), it occurs during the first two thirds of gestation, accounts for most of the conceptus-free increase in maternal body weight, and is directly related to maternal hyperphagia, as it disappears with food restriction (12).

The increase in maternal fat depots seems to be mainly a result of enhanced lipogenesis, which has been demonstrated both *in vivo* (13) and in periuterine adipose

tissue *in situ* (14); it corresponds to an increase in the synthesis of both fatty acids and glyceride glycerol, indicating that triglyceride synthesis is enhanced.

The tendency to accumulate fat in the mother ceases during the last trimester of gestation (5,10,15), when maternal lipid metabolism switches to a catabolic state because of the coincidence of several changes taking place in her adipose tissue metabolism at this time: (a) The augmented lipogenic activity decreases rapidly (14); (b) lipolytic activity becomes highly enhanced (16) because of increased activity by the key enzyme in the lipolytic cascade, hormone-sensitive lipase (HSL) (17); and (c) tissue uptake of circulating triglycerides decreases (6) because of reduced lipoprotein lipase (LPL) activity (18,19). The adipose tissue HSL-to-LPL messenger RNA and activity ratios appear enhanced during late gestation (17), indicating that net triglyceride breakdown is augmented.

Enhanced adipose tissue lipolytic activity increases the release of both FFA and glycerol into the maternal circulation, where they reach high concentrations in the plasma (16,17). Placental transfer of these two lipolytic products is low (3), and maternal liver is their main receptor (20). As shown in Fig. 1, after being converted in the liver into their respective active forms, FFA to acyl-CoA and glycerol to glycerol-3-phosphate, they may be used for esterification in triglyceride synthesis, or for ketone body production in the case of FFA, or glucose synthesis in the case

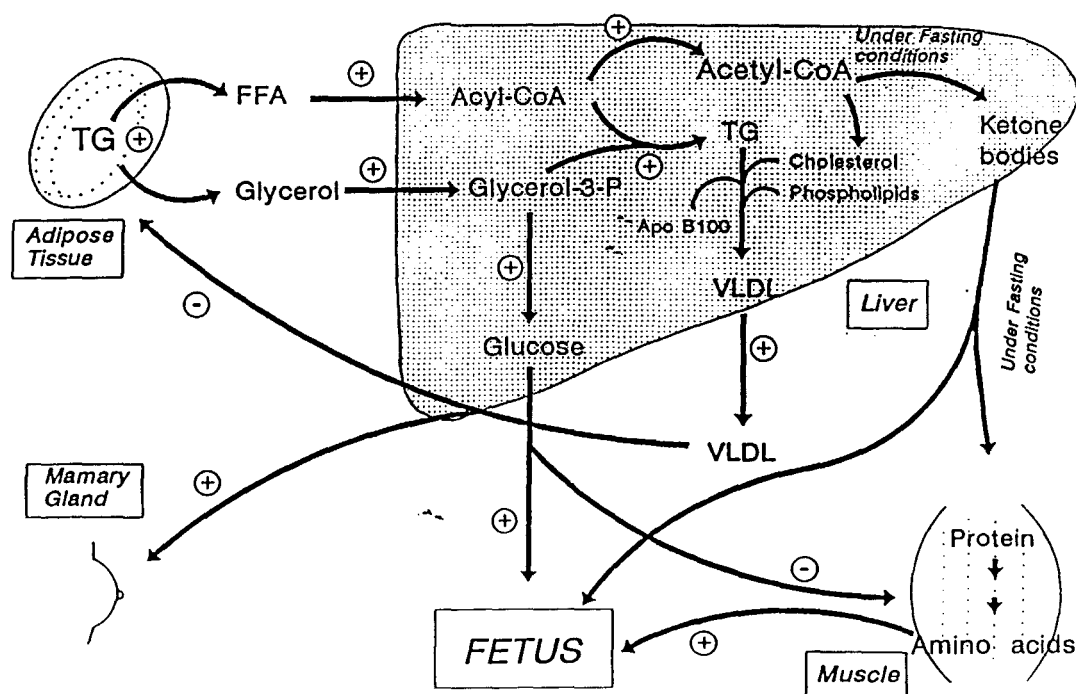


FIG. 1. Major changes in lipid metabolism taking place during late gestation. At this stage, adipose tissue lipolysis becomes a major source of substrates for gluconeogenesis, ketogenesis, and triglyceride synthesis. Glucose and amino acids are essential metabolites for the fetus and continuously cross the placenta, whereas ketone bodies diffuse to the fetus only under maternal fasting conditions, when ketogenesis becomes highly accelerated. +, enhanced pathway; -, inhibited pathway. TG, triglyceride; Apo B-100, apoprotein B-100; VLDL, very-low-density lipoproteins.

of glycerol. All these pathways seem to become enhanced during late gestation. We previously showed that glyceride glycerol synthesis from glycerol is very efficient in the liver of the fed, 21-day pregnant rat (21), and this—together with the increased transfer of FFA and glycerol to the liver from adipose tissue lipolysis—justifies the enhanced esterification and subsequent release in the form of very-low-density lipoprotein (VLDL) triglycerides by the liver, a process that is also known to be enhanced during late pregnancy (22) (Fig. 1). Ketone body synthesis becomes highly enhanced during late pregnancy under fasting conditions (6,18,23), and the use of ketone bodies by certain maternal tissues reduces their consumption of glucose, which is therefore saved for transfer to the fetus. During late gestation, gluconeogenesis from glycerol is highly augmented under both fed and fasting conditions, and this gluconeogenesis is even more efficient than that from other classic gluconeogenic substrates, such as alanine or pyruvate (24,25). It is therefore proposed that the preferential consumption of glycerol for gluconeogenesis spares the use of other possible substrates, such as amino acids, which are more essential for the fetus (Fig. 1).

We may then conclude that besides the availability of essential fatty acids from maternal circulation, the fetus greatly benefits from the end metabolic products of maternal adipose tissue lipolytic activity. Ketone bodies freely cross the placenta (3) and may be used as fetal fuels (26) or even as substrates in brain lipid synthesis (27). The efficient transfer of glucose to the fetus (1,2) and the use of glycerol as a preferential gluconeogenic substrate also benefit the fetus under conditions of reduced availability of other substrates, such as amino acids (1,25,28). Finally, the active adipose tissue lipolytic activity during late gestation also benefits maternal tissues, as at this stage tissue utilization of glucose is greatly decreased because of insulin resistance (29), and the lipolytic products—especially FFA and ketone bodies—can be used as alternative fuels to spare glucose.

MATERNAL HYPERLIPIDEMIA

During normal pregnancy, there is a consistent increase in plasma triglycerides, with smaller rises in phospholipids and cholesterol (7); as shown in Fig. 2, such change corresponds to a specific proportional enrichment of triglycerides in the lipoprotein fractions (30,31), including the low-density lipoproteins (LDL) and high-density lipoproteins (HDL), which normally transport them in very small proportion. Even within the HDL subfractions, there is a specific increment in the proportion of the triglyceride-rich HDL_{2b} subfraction in women during gestation, whereas the proportion of those such as HDL_{2a} or HDL₃, which are poor in triglycerides, is reduced (31). However, the greatest absolute change in plasma triglycerides during gestation corresponds to the VLDL triglycerides (30). These lipoproteins are synthesized in the liver, and the triglycerides that they carry must be derived from the fatty acids and glycerol that are either synthesized within the liver or reach it from

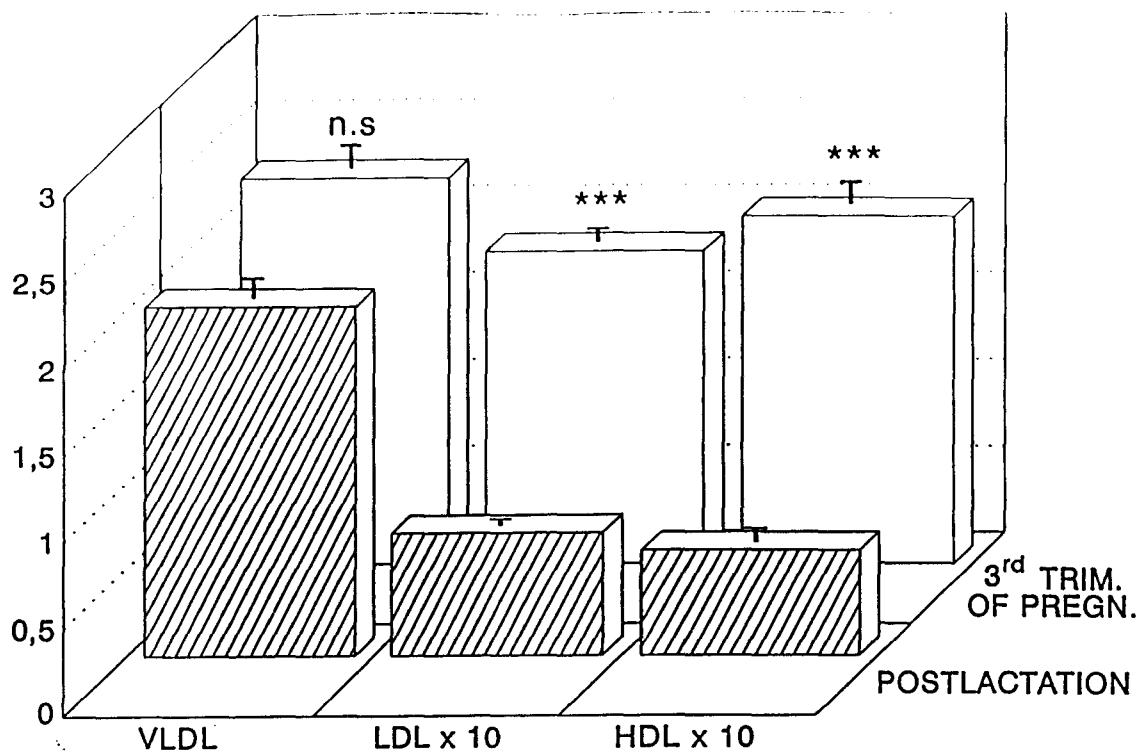


FIG. 2. Plasma lipoprotein triglyceride-to-cholesterol ratio in women during pregnancy and at the end of the lactation period. Asterisks correspond to the statistical comparison between values at the third trimester of gestation and at postlactation. *** $p < .001$. Adapted from Montelongo *et al.* (30).

the circulation after being released by adipose tissue lipolysis (Fig. 1), which is highly augmented during late gestation, as described above.

Enhanced liver production of VLDL triglycerides and their decreased removal from the circulation as a result of reduced adipose tissue LPL activity, which is consistently seen during late gestation (17,19,31), seem to be the main factors responsible for the increase in VLDL triglycerides during gestation.

The abundance of VLDL triglycerides in the mother's plasma during gestation, together with other factors summarized in Fig. 3, may contribute to the accumulation of triglycerides in the other lipoproteins. One of these factors is the increase in cholesteryl ester transfer protein (CETP) activity, which was recently found at mid-gestation (31,32). CETP catalyzes the net mass transfer of triglycerides from VLDL towards triglyceride-poor lipoproteins, LDL and HDL, whereas net mass transfer of cholesteryl ester occurs in the opposite direction, from LDL and HDL towards VLDL; at the same time, LDL and HDL exchange neutral lipid molecules without significant net mass transfer. The increase in the activity of this protein must therefore contribute to the proportional enrichment of triglycerides seen in LDL and HDL during gestation. Another factor contributing to this same effect may be the decrease in the activity of hepatic lipase, which is also seen during late gestation (31). This enzyme controls the conversion of buoyant HDL₂ triglyceride-rich particles into small HDL₃ triglyceride-poor particles, and therefore its decreased activity allows

a proportional accumulation in the former, as has been shown during late gestation (31) (Fig. 3).

Among the hormonal factors that are normally modified during gestation, two seem to be responsible for most of these changes. The first is the insulin-resistant condition constantly present during late gestation, which we have recently found contributes to, or is responsible for, both the enhanced adipose tissue lipolytic activity and the decreased LPL activity (29,33). We have seen above that these two changes contribute to both the enhanced availability of substrates for the liver synthesis of triglycerides and the decreased removal from circulation of VLDL triglycerides. The second factor is the progressive increase in plasma estrogen levels during gestation (30,31); this is known to enhance the liver production of VLDL and to decrease hepatic lipase activity, and therefore it actively contributes to several of the changes in lipoprotein metabolism occurring during gestation that end with the development of an exaggerated hypertriglyceridemia (reviewed in ref. 7).

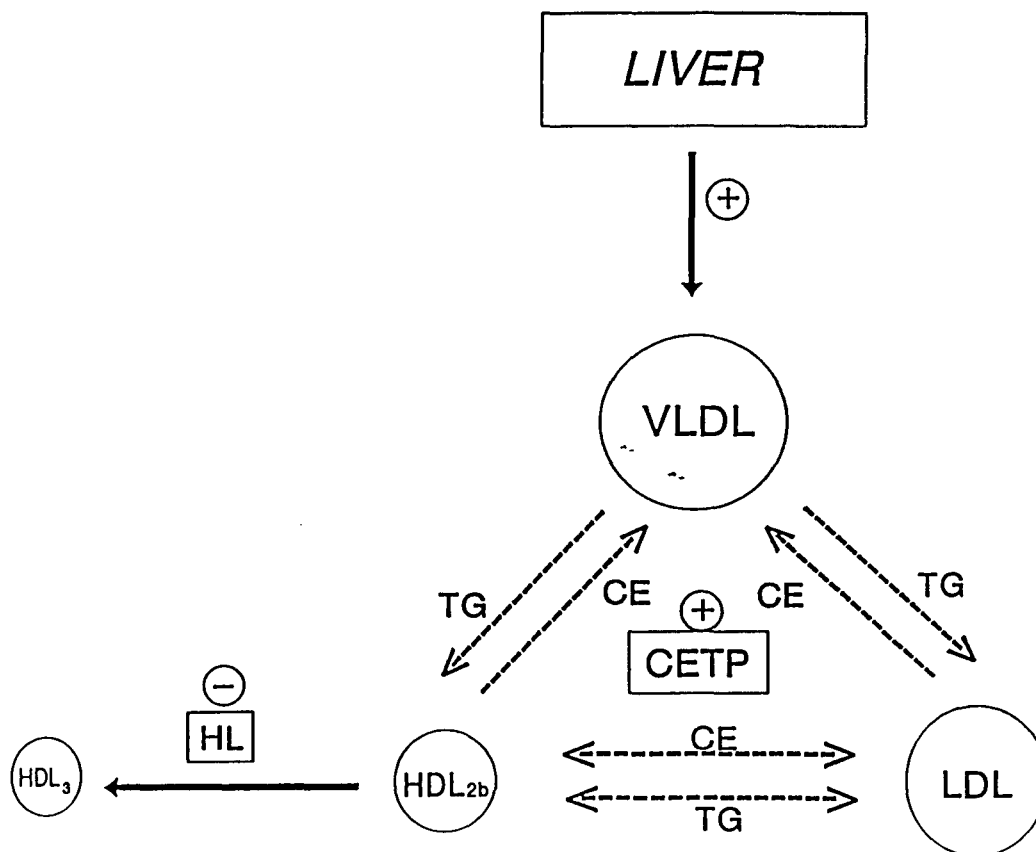


FIG. 3. Proposed factors contributing to the proportional accumulation of triglycerides (TG) in the main circulating lipoproteins during late pregnancy. An enhanced liver production of VLDL seems to be the main factor yielding an increase in plasma VLDL levels. The enhanced CETP activity occurring at midgestation (31,32) facilitates the net mass transfer (*single dotted arrows*) of triglycerides by cholesteryl esters (CE) from VLDL towards lipoproteins of higher density, LDL and HDL, which are poor in TG. Besides this, LDL and HDL can also exchange neutral lipid molecules (*double arrows*) without significant net mass transfer. Because hepatic lipase (HL) activity catalyzes the conversion of triglyceride-rich HDL_{2b} subfractions into HDL₃, which is poor in TG, the decrease of HL seen during gestation (31) would facilitate the accumulation of the former.

BENEFITS OF MATERNAL HYPERTRIGLYCERIDEMIA FOR THE OFFSPRING

Although triglycerides do not cross the placental barrier (3), there are a few mechanisms by which both the fetus and the newborn could benefit from maternal hypertriglyceridemia.

1. Although the liver of the adult rat normally lacks LPL activity, we have consistently seen an intense increase in LPL activity in the liver of the 24-hours fasted, 20-day pregnant rat (18,34,35). This activity may be the result of LPL washout from extrahepatic tissues carried by the triglyceride-rich lipoprotein remnants reaching the liver. Through this mechanism, the liver of the fasted pregnant rat switches from being a triglyceride-exporting organ to being a triglyceride-accepting one, allowing the use of circulating triglycerides as substrates for ketone body synthesis. In this way, ketogenesis in the maternal liver in late gestation becomes highly enhanced under fasting conditions (6,18,23), and this, besides being a mechanism for decreasing glucose use by maternal tissues, directly benefits the fetus by allowing it to obtain ketone bodies through the placenta (see above).

2. Another mechanism by which the fetus may benefit from maternal hypertriglyceridemia is the availability of essential fatty acids from maternal triglycerides. The lipase activities in the placenta hydrolyze maternal triglycerides, and the released FFA can reach the fetus for reconversion into triglycerides.

3. An additional benefit for the offspring of maternal hypertriglyceridemia during gestation is its active contribution to milk synthesis in preparation for lactation (36). Using late-pregnant rats, we showed that there is a rapid appearance of labeled lipids in the mammary gland after an oral load of labeled triglycerides (37), and blocking the increase in mammary gland LPL activity by treatment with progesterone in the late-pregnant rat completely inhibits the decline in plasma triglycerides normally occurring near parturition (38). These findings show that the rapid and intense increase in mammary gland LPL activity that occurs before parturition, at a time when LPL activity in adipose tissue is very low (17,35,38,39), drives circulating triglycerides from the adipose tissue to the mammary gland (Fig. 1) and facilitates the clearance of triglycerides from circulation and their use in milk synthesis. Through this mechanism, essential fatty acids from the mother's diet that circulate in the form of triglycerides become available to the suckling newborn.

EFFECT OF DEVIATIONS IN MATERNAL HYPERLIPIDEMIA TO FETAL GROWTH

The importance of maternal hyperlipidemia to fetal growth may be studied by determining how deviations in this hyperlipidemia affect fetal development.

Treating pregnant rats with fluvastatin, an inhibitor of cholesterol synthesis that does not seem to cross the placental barrier but provokes hypocholesterolemia in the mother, has been shown to reduce fetal weight and even greatly decrease fetal

viability (40). Additionally, treating pregnant rats with a nonabsorbable bile acid-binding resin (cholestyramine), which enhances cholesterol synthesis through induction of the key enzyme for this pathway (3-hydroxy-3-methylglutaryl coenzyme A reductase), has also induced the enzyme activity in fetal liver (41). These findings therefore show that fetal growth and metabolism are sensitive to perturbations in maternal lipoprotein metabolism.

Under more physiologic conditions, we have recently found that a sucrose-rich diet in the pregnant rat causes exaggerated hypertriglyceridemia, and this effect is associated with an accumulation of triglycerides in the placenta, an increase in the placental LPL activity, and—what is more important—a significant reduction in fetal weight (42). The possibility then exists that the exaggerated maternal hypertriglyceridemia caused by the sucrose-rich diet—which mainly corresponds to endogenously synthesized fatty acids—has saturated the placental fatty acid transfer process, impeding the adequate transfer of essential fatty acids to the fetus and consequently impairing normal fetal growth.

Although the above reasoning implies that some deviations in maternal hyperlipidemia may cause major alterations in fetal development, there are conditions of maternal hypercholesterolemia that do not seem to affect fetal growth. Pregnant women with pre-existing hypercholesterolemia have been reported not to have problems in the outcome of their pregnancy (43,44).

To study further this apparent protection of fetal development under conditions of maternal hypercholesterolemia, we examined the effects of a cholesterol-rich diet in the pregnant rat. As shown in Fig. 4, plasma cholesterol was greatly enhanced during gestation in rats receiving a standard diet supplemented with 2% cholesterol and 1% cholic acid to facilitate cholesterol absorption, whereas their plasma triglycerides were only mildly, but significantly, augmented in comparison with the values found in pregnant rats fed the standard diet. Regardless of the mechanism responsible for these changes, which is beyond of the scope of this chapter, the outcome of pregnancy in rats receiving the cholesterol-rich diet did not differ from that of the rats under the standard diet, as indicated by an unchanged number of fetuses and the normal weights of both placentae and fetuses (data not shown).

Fetal protection against maternal hypercholesterolemia may be a consequence of the impermeability of the placenta to cholesterol transfer. This has been a question of controversy; early studies have suggested an important contribution of maternal cholesterol to fetal plasma and tissue cholesterol accretion (45), whereas more recent reports have found a minimal transfer of maternal cholesterol (46,47). However, no direct studies investigating this problem have been carried out as yet. In any case, any placental transfer of cholesterol would have to depend on its concentration on the maternal side, and differences such as those caused by a cholesterol-rich maternal diet would have to alter the concentration of lipids in fetal plasma. However, as also shown in Fig. 4, plasma concentrations of cholesterol and triglycerides in fetuses from dams on a cholesterol-rich diet do not differ from those of fetuses from control mothers. The fetal plasma lipoprotein profile is very similar in both groups, whether the mothers received the cholesterol-rich diet or not (data not shown). These findings

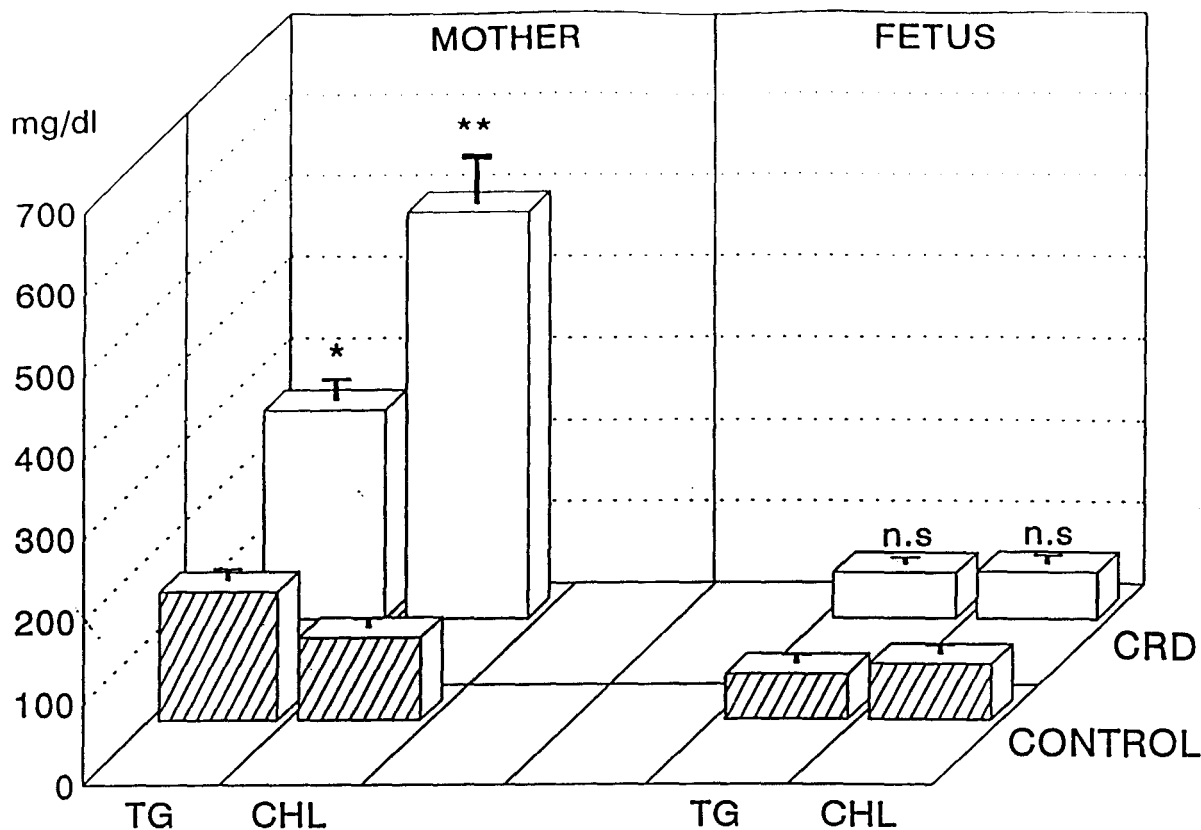


FIG. 4. Effect of feeding pregnant rats with a diet supplemented with 2% cholesterol and 1% cholic acid on plasma lipid concentrations in mothers and fetuses at day 20 of gestation. Asterisks correspond to the statistical difference between rats receiving or not receiving the cholesterol-rich diet. * $p < .05$; ** $p < .01$.

therefore support the concept that at least in the rat, cholesterol requirements during fetal life are met by fetal cholesterol synthesis rather than by placental transfer, and maternal hypercholesterolemia affects neither the fetal lipid profile nor fetal development, thanks to the lack of transfer of maternal cholesterol through the placenta. On the basis of the lack of alteration in the gestational outcome of hypercholesterolemic women (43,44), it seems reasonable to assume that such a conclusion is also valid in humans.

We may then conclude that whereas conditions that cause either maternal hypocholesterolemia or exaggerated hypertriglyceridemia greatly affect fetal growth and even viability, conditions of exaggerated hypercholesterolemia do not affect the outcome of pregnancy, probably as the result of the impermeability of the placenta to maternal cholesterol.

SUMMARY AND CONCLUSIONS

During gestation, the increase in the mass of maternal structures mainly corresponds to an accumulation of depot fat, which occurs during the first two thirds of gestation, has a direct relation to maternal hyperphagia, and is a consequence of

enhanced adipose tissue lipogenesis. During the last trimester of gestation, maternal lipid metabolism switches to a catabolic condition that leads to a net breakdown of fat depots, thereby increasing the release of FFA and glycerol into the circulation. Placental transfer of these lipolytic products is low and they are dealt with by the maternal liver, where they are either re-esterified for the synthesis of triglycerides, which are released back into the circulation in the form of VLDL, or are oxidized for the synthesis of ketone bodies (FFA) or preferentially transformed into glucose (glycerol). All these pathways are enhanced during late gestation, although ketogenesis is stimulated only under fasting conditions. Enhanced liver production of VLDL triglycerides in the presence of decreased extrahepatic LPL activity, which restrains their removal, causes an exaggerated increase in these lipoproteins. This, together with an increase in CETP activity, facilitates the transfer of triglycerides from VLDL to higher-density lipoproteins, causing a proportional enrichment of triglycerides in all the main circulating lipoproteins.

Despite the impermeability of the placenta to triglycerides, maternal hypertriglyceridemia benefits the offspring in several ways: (a) under fasting conditions, the liver of the mother shows increases in LPL activity, becoming an acceptor organ for circulating triglycerides that are used as substrates for ketone body synthesis, and these compounds easily diffuse through the placenta and are used by the fetus; (b) the presence of lipase activities in the placenta makes essential fatty acids from maternal triglycerides available to the fetus; and (c) the induction of LPL in mammary gland around parturition drives circulating triglycerides to this organ for milk synthesis. Although certain deviations in maternal hyperlipidemia may affect fetal growth, as shown under conditions of hypocholesterolemia or exaggerated hypertriglyceridemia, conditions of hypercholesterolemia do not affect the outcome of pregnancy, probably because of the impermeability of the placenta to maternal cholesterol. It may then be concluded that whereas maternal hyperlipidemia is a constant feature of normal pregnancy and a necessary condition for the continuous availability of substrates to sustain fetal growth, the poor placental transfer of lipids protects the fetus from some—although not all—of the variations in their levels in maternal plasma.

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DISCUSSION

Dr. Page: Am I right in thinking that placental lipoprotein lipase does not attack chylomicrons?

Dr. Herrera: No, it attacks chylomicrons as well as VLDL triglycerides. Lipoprotein lipase in the placenta does not differentiate between VLDL and chylomicrons.

Dr. Page: Is there any effect of things like estradiol on placental lipoprotein lipase activity?

Dr. Herrera: I don't think so. We have not measured it, but we don't think that there is any effect. We measured lipoprotein lipase activity in adipose tissue of pregnant rats after estradiol administration and found no change.

Dr. Battaglia: If you take a very thin and a very fat pregnant rat, what changes between those two in these adaptations? In other words, how does obesity transform the normal metabolic adaptations to pregnancy?

Dr. Herrera: We did not study obesity, because overfeeding the rats changes the situation too much. With undernutrition in the rats that were kept in a food-restricted condition during pregnancy, there was no increase in liver triglycerides, there was no increase in liver lipoprotein lipase activity, and hyperlipidemia was much more moderate (1). That is why we saw then the possibility of explaining the uptake of triglycerides by the liver of the fasting pregnant rat by the action of the lipoprotein lipase that appears in the liver as a result of the washout of extrahepatic lipoprotein lipase molecules by remnants of triglyceride-rich lipoproteins (2,3).

Dr. Cedard: You explain that the increase of estradiol during pregnancy increases the number of LDL receptors, and this justifies that pregnancy does not enhance the hypercholesterolemic condition of patients having familial hypercholesterolemia. However, another explanation could be the presence in the placenta of a specific receptor for low-density lipoproteins, which are then transformed into progesterone; there are also specific receptors for acetyl lipoprotein, as in macrophages, and also less specific receptors for HDL, although it is possible that the lipoproteins are kept in the placenta and transformed either into steroids or structural components.

Dr. Herrera: The placenta does not affect lipoprotein production. That is modulated by estrogen, but the placenta has lipoprotein receptors, and lipoproteins are taken up from the maternal circulation. This is why I say that one of the physiologic roles of maternal hyperlipidemia is probably to allow enough substrate to be taken up by the placenta for the synthesis of progesterone for steroid hormones.

Dr. Marconi: We know that the second child is usually bigger than the first. Do you think that this could be explained by the fact that insulin resistance increases with further pregnancies?

Dr. Herrera: Maybe. It is true that in the second pregnancy, there is a greater tendency for the mother to be hyperglycemic, so probably there is also a greater amount of glucose crossing the placenta and more possibility for fetal pancreatic β cells to respond to it. Fetal insulin acts as a growth factor, and such a mechanism could contribute to the tendencies of developing fetal macrosomia after several pregnancies.

Dr. K. Taher: I think that as the number of pregnancies increases the insulin sensitivity decreases; that is why maternal diabetes becomes more prevalent with successive pregnancies and why the size of the baby also increases. Have you any comment on that?

Dr. Herrera: Although that is a true fact, we don't know yet its mechanism. Insulin resistance in late pregnancy is caused by several factors, including the presence of counterregulatory hormones and maternal hyperlipidemia, and these factors may be aggravated in successive pregnancies.

Dr. Talamantes: We are doing some studies looking at the effect of placental lactogen on the sensitivity of the mammary gland. With every succeeding pregnancy the mammary gland becomes more sensitive to the actions of prolactin to make casein or fatty acid, so there is an alteration between the first pregnancy and the second and third pregnancies. The mammary gland becomes much more sensitive to the action of hormones, so there is an increased sensitivity that is very interesting. The underlying cause has yet to be determined.

Dr. Herrera: Insulin resistance occurs in many maternal tissues, but it doesn't appear in mammary gland (4,5). Mammary gland responds to insulin in the late-pregnant rat in the same way as in virgin control animals, and it contributes together with prolactin to the induction of lipoprotein lipase and the other metabolic changes in this specific organ (5,6).

Dr. Nicolaidis: We have found that in normal pregnancy there is an exponential decrease in fetal triglyceride levels with gestation, especially after 24 weeks, and that corresponds with increased laying down of fat in the fetus, and in hypoxemia in placental insufficiency the fetal triglyceride levels remain high. We thought the explanation for that was that hypoglycemia mediated hypoinsulinemia, resulting in reduced lipoprotein lipase activity in the fetus, so that was the explanation for fetal hypertriglyceridemia. But I was surprised that on the maternal side the triglyceride levels were normal. And yet you have all these massive efforts for the maternal side to increase triglycerides, but if they are not taken away by the placenta, where do they go?

Dr. Herrera: To the mammary gland, being mediated by the induction of lipoprotein lipase activity occurring in this organ around parturition (7,8).

Dr. Nicolaidis: To the mammary gland? So the mothers are producing more milk to feed their growth-retarded babies after birth!

Dr. Herrera: We don't have experience on this specific point.

Dr. Pardi: It is a clinical but important point; perhaps you have data about lactation in growth retardation. In my opinion, the capacity for lactation is decreased in parallel with the degree of placental insufficiency.

Dr. Nicolaidis: I haven't any data, but it sounds logical. I have certainly not observed increased lactation in women with growth-retarded babies.

Dr. Herrera: There is also a curious situation concerning hypercholesterolemic pregnant women. Some of these women have familial hypercholesterolemia, which does not worsen during pregnancy. On the contrary, there are some reports saying that plasma cholesterol is decreased because there is induction of LDL receptor caused by the increased estrogen level (9).

Dr. Godfrey: Just to follow on Dr. Marconi's suggestion—it is a nice idea. The epidemiologic data, such as they are, are that if you use maternal fatness—body mass index or perhaps more importantly regional body fat distribution—as a proxy for insulin resistance, the increment in fetal growth associated with increasing parity cannot be explained by maternal fatness.

Dr. Nicolaidis: Could you just explain that in a simple way?

Dr. Godfrey: Multiparous women don't have bigger babies simply because they are fatter. And to follow on from that, there are profound changes in regional body fat distribution in human pregnancy, even dating back before the 16 week cutoff in your slide. I was wondering if you had any data from your rat studies, in which I am sure regional body fat distribution is more difficult to study.

Dr. Herrera: No, we did only total carcass analysis (10). An important point is that before the decline of lipoprotein lipase activity in adipose tissue, there is an increase in lipogenesis in adipose tissue (11). Unlike hepatic lipase activity, lipoprotein lipase activity declines only during late gestation (12), when fat is already distributed in the different organs. It seems then that such change plays a role mainly in the preparation of the mother for parturition rather than in the distribution of the accumulation of fat.

Dr. Battaglia: Do we have any long-term data that show differences between women who had no children or one child vs. those who have had four children, in terms of later obesity or later complications related to fat metabolism?

Dr. Campbell: The old data from Frank Hytten's group suggested that women did not get fatter with successive pregnancies, looking from para I to II to III, probably up to about para IV, except for a very small number of women who were obese to start with, but they only got fatter with one particular pregnancy, not with each one. So it was not entirely clear from the epidemiologic data what exactly was happening (13).

Dr. Godfrey: From our follow-up studies of 25,000 to 30,000 people whose birth records we have, we found no effects of parity in relation to cardiovascular disease or diabetes in the offspring. In other words, we do not find that men and women who were firstborn or secondborn have any difference in their rates of coronary heart disease or diabetes 50 or 60 years later.

Dr. Van Assche: The adaptation concerning the lipids may not be so important in succeeding pregnancies, but the vascular adaptation is certainly not so good in the first pregnancy, improves in the second and the third, and then maybe deteriorates again in the fourth and fifth. So the change in birth weight is caused by other factors, and the cardiovascular adaptation can be even more important than the metabolic adaptation.

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