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LIPID METABOLIC INTERACTIONS IN THE MOTHER DURING PREGNANCY AND THEIR FETAL REPERCUSSIONS

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LIPID METABOLISM IN THE MOTHER

Aside from the products of conception, maternal body weight increase during gestation corresponds to increased mass in certain maternal structures and a specific accumulation of fat, as shown both in human pregnancy (1) and in the rat (2-4). This fat accumulation occurs during the first part of gestation (2,4) and is related to both maternal hyperphagia, since it is not found in food restricted (5,6) or food deprived rats (2,7), and enhanced lipogenesis and unmodified or even augmented extrahepatic lipoprotein lipase (8,9). The tendency to accumulate fat ceases during late gestation (1,2,4) because the maternal lipid metabolism changes to a catabolic condition as shown by the increased lipolysis (10, 11) and the reduced circulating triglycerides uptake by adipose tissue (12). The latter is a consequence of reduced adipose tissue lipoprotein lipase activity (4,13-15). These changes, together with the hepatic overproduction of triglycerides (16-18) and enhanced absorption of dietary lipids (19) boosts the circulating triglyceride concentration in the mother during late gestation (4,8,13,20-26).

Table 1. Plasma lipidic components in 20-day pregnant and nonpregnant rats

	VIRGIN	20-DAY PREGNANT
FFA (μM)	282±24	438±49**
Glycerol (μM)	81±16	152±21*
Triglycerides (mg/dl)	77±6	390±61***
VLDL-triglycerides (mg/dl)	38±7	233±25***

Determinations were carried out as previously reported (4). Mean ± SEM; n = 5-8 rats/group. Statistical comparison of pregnant and virgin rats: *p<0.05; **p<0.02; ***p<0.001.

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The combined changes occurring in maternal adipose tissue, liver and intestinal activity during late gestation are responsible for the increments in circulating lipid metabolites concentration. As shown in Table 1, in the 20-day pregnant rat plasma level of free fatty acids (FFA), glycerol and triglycerides are greatly enhanced as compared to age and sex matched virgin controls. As also shown in Table 1, maternal hypertriglyceridemia mainly corresponds to an increase in circulating VLDL-triglycerides, the values of which parallel the increase found in plasma triglycerides in the same animal. However rising levels of chylomicrons in circulation may also contribute to maternal hypertriglyceridemia.

Enhanced plasma VLDL-triglyceride concentrations during late pregnancy in both the rat and human agree with several previous reports including our own (4,26). However, it is not well established whether this change implies an alteration in the intrinsic composition of the VLDL particles or a change in their number. We previously found an enhanced triglycerides/cholesterol ratio and a modified elution profile from heparin-Sepharose column chromatography of VLDLs from 20-day pregnant rats as compared to virgin controls (4,12). Because these differences may also imply different metabolic behaviour of these VLDL particles, the subject is evaluated below.

As shown in Figure 1, the percent composition of VLDL particles remain unchanged in 20-day pregnant rats despite the increase in lipoprotein concentration comented above. As shown in Figure 2, VLDL diameter and particle mass do not differ between 20-day pregnant rats and virgin controls, whereas ther seem to be differences in the apoprotein content. As also shown in Figure 2, it appears that, apo E/apo C-II and apo E/apo C-III ratios are lower in VLDL from 20-day pregnant rats whereas apo C-II/apo C-III ratio is higher than in those from virgin controls.

Since differences in the apolipoprotein content in lipoprotein particles could affect their efficiency as substrates for specific enzymes (27) and their consequent catabolism, the differences we found in the VLDL apoprotein composition between pregnant and virgin rats forced us to examine whether there were also differences in their behaviour as substrates for the two immediate key enzymes of their catabolism, lipoprotein lipase and hepatic lipase (28). As shown in Figure 3, it appeared that when the same amount of VLDL-triglycerides from 20-day pregnant and virgin rats were offered either to the purified lipoprotein lipase or to

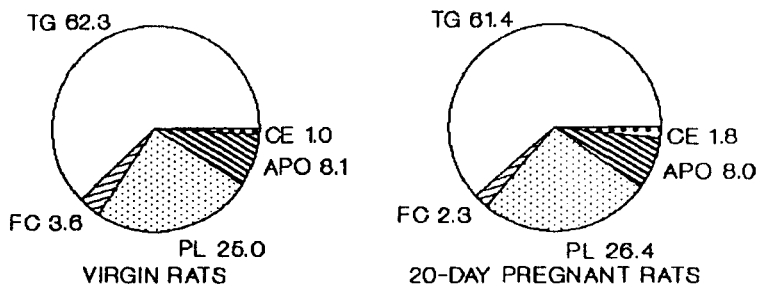

Fig. 1. Percent composition of rat VLDL. Values correspond to a pool of plasma coming from 4 rats/group. TG= Triglycerides; FC= Free cholesterol; CE= Cholesteryl esters; PL= Phospholipids; Apo= Apoproteins. VLDL were isolated by sequential ultracentrifugation for the corresponding determinations as previously shown (4).

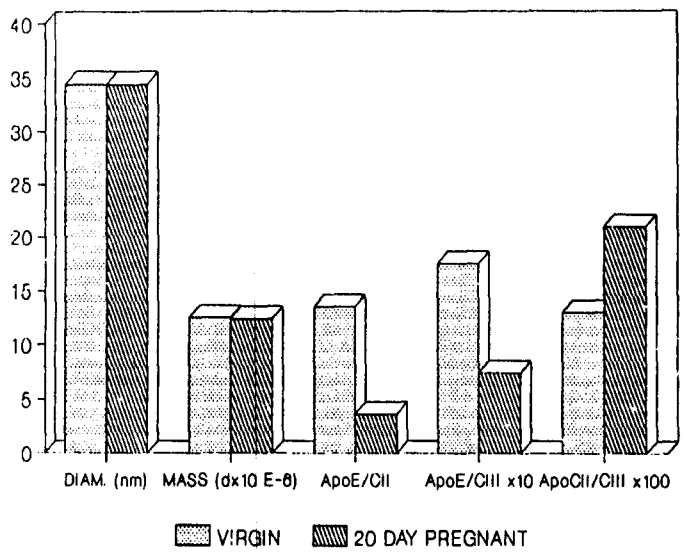

Fig. 2. Diameter, mass and apoprotein ratios of VLDL from virgin and 20-day pregnant rats. VLDL particle diameter and mass were estimated (121) by assuming that they are spherical. For apoprotein determinations VLDL were delipidized with acetone:ethanol (1:1 by vol) and proteins resuspended in 0.01 M Tris pH 8.6 containing 8 M urea and 0.01 mM dithiothreitol. Sixty to eighty μg of VLDL protein were applied to 7.5% acrylamide gels containing ampholytes pH 4-6.5, which were run at 2000 V for 150 min. After staining with Coomassie brilliant blue R-250, the gels were used for densitometric scanning at 560 nm in a Beckman DU-8 spectrophotometer. Relative areas of each band were used to calculate the apoprotein mass ratios.

the hepatic lipase, their respective hydrolitic efficiency was very similar with substrate coming from either rat groups. Actually, although no statistical comparison between the groups is given, it appeared that in the case of lipoprotein lipase the amount of VLDL-triglycerides hydrolized is even slightly higher when the particles came from pregnant rather than virgin rats (Figure 3), clearly indicating that the catalytic efficiency of this enzyme is by no means reduced in the former. We may therefore conclude that abundance of VLDL particles in maternal circulation during late pregnancy is not a consequence of their modified apoprotein composition, which could have altered their characteristics as adequate substrates for the enzymes responsible for their catabolism. They are, however, an adequate floating lipidic source for use wherever required (see below).

Consequences on Late Gestation of Maternal Lipidic Accumulation During the First Half of Pregnancy

We believe that changes in lipid metabolism during late gestation are not only a direct consequence of the metabolic adaptations occurring during that stage but may also be extensively influenced by the maternal capacity to accumulate lipid stores during the first half of pregnancy. There are no previous studies to directly support this hypothesis, but we had carried out two different experiments that are consistent with it. The first one corresponds to unpublished data from our recently reported study with thyroidectomized pregnant rats (29).

As shown in Figure 4, increments in both conceptus-free maternal body and liver weights during the first 12 days of gestation are greatly impaired in pregnant thyroidectomized rats not receiving thyroid hormone treatment. Such reduction in the mass of maternal structures in hypothyroid pregnant rats is maintained until the end of the gestational period even when rats are treated with daily substitution doses of thyroid hormones (1.8 μg of thyroxine/100 g body wt.) from day 12 of gestation to term (Figure 4). At day 21 of gestation these animals are known to show significant reductions in fetal weight (29) and in maternal circulating triglyceride concentration as well as an impaired capacity to mobilize endogenous fat depots with starvation (unpublished results). As also shown in Figure 4, when animals were hypothyroid only during the second half of gestation (from day 12 to day 20) no reductions in both maternal liver and conceptus-free weights were found as compared to thyroidectomized rats receiving the thyroxine substitution treatment for the whole period (from day 0 to day 20 of gestation). These data indicate that sufficient maternal stores during the first half of gestation are required to sustain maternal structures and hypertriglyceridemia and to fulfill metabolic needs during late pregnancy including the adequate availability of substrates for the fetus.

Figure 5 summarizes a second experiment that was addressed in establishing the role of increased fat accumulation during the first part

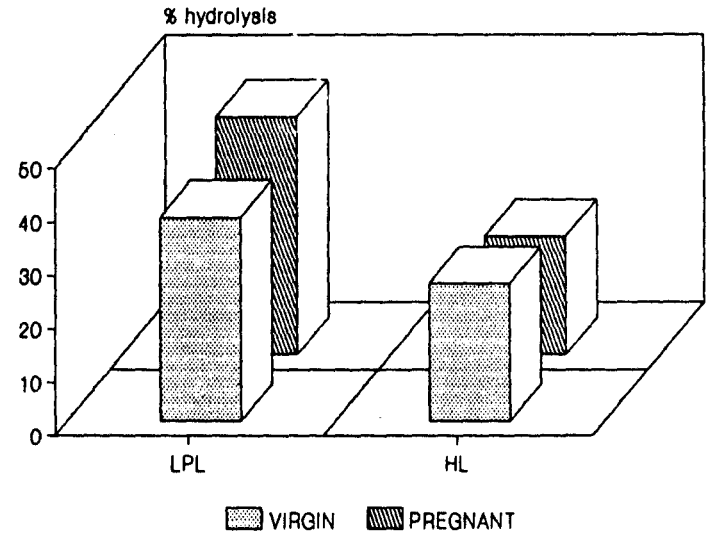

Fig. 3. Hydrolysis of tri(^{3}H)-olein labelled VLDL from virgin and 20-day pregnant rats by purified lipoprotein lipase (LPL) and hepatic lipase (HL). Purified VLDL from a pool of plasma from 5 virgin or from 20-day pregnant rats were labelled *in vitro* with tri(^{3}H)-olein (122) and amounts corresponding to 82 or 90 nmoles/ml of triglyceride from each preparation were respectively incubated at 37°C for 2 h in the presence of either lipoprotein lipase or hepatic lipase purified from human post-heparin plasma by heparin-Sepharose affinity chromatography. Hydrolysis was estimated as the appearance of ^{3}H-free fatty acids in the media, and expressed as % of the initial tri (^{3}H)-olein.

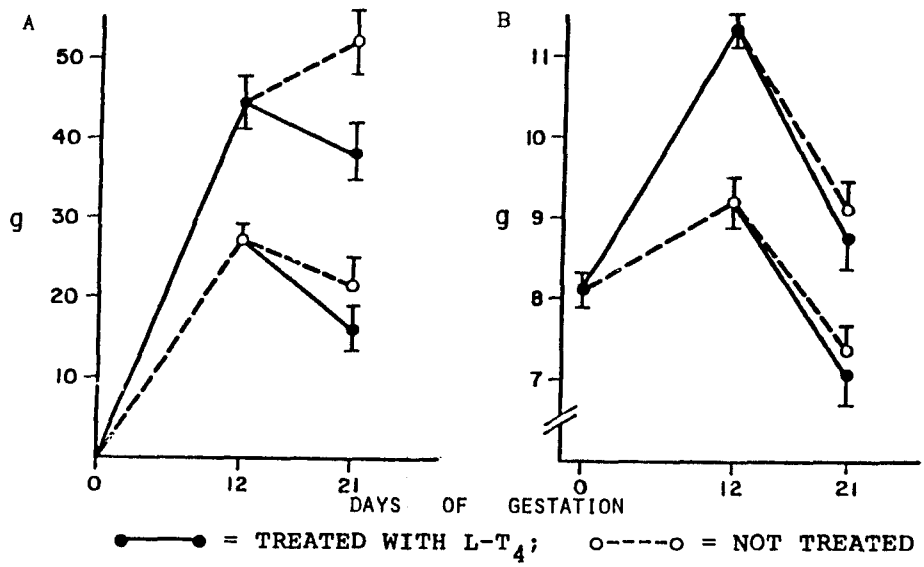

Fig. 4. Conceptus-free maternal body weight (A) and liver weight (B) in untreated thyroidectomized rats (o---o) or rats treated with 1.8 μg thyroxine/100 g body wt for different gestational periods (●——●). Rats weighing 180-200 g were surgically thyroidectomized at day 0 of gestation (the day that sperm appeared in vaginal smears) and intraperitoneal treatments with either thyroxine or saline were given, starting the day after surgery during the days indicated in the Figure.

of pregnancy in the metabolic adaptations occurring during late gestation. Rats were made diabetic by the intravenous administration of streptozotocin (45 mg i.v./Kg body wt.) prior mating, at which time they were divided into three groups: 1) *Controls*, which received a daily subcutaneous replacement insulin therapy (1.5 IU/100 g body weight); 2) *D12-20* that received such treatment from day 0 until the 12th day of gestation, being kept diabetic between days 12 and 20 ; or 3) *D* that did not receive any treatment throughout pregnancy. All animals were studied at day 20th of gestation. As shown in Figure 5, when compared to *Controls*, both *D* and *D12-20* rats were highly hyperglycemic, although, as expected, blood glucose levels were higher in the former. Lumbar fat pad weight was, however, greatly reduced in animals from group *D* and stable in those from group *D12-20*, indicating that diabetes during the first half of gestation, but not during the second, impairs maternal capacity to maintain augmented lipidic stores.

As also shown in Figure 5 plasma triglyceride levels were greatly augmented in both *D* and *D12-20* animals. The values in the latter were even higher than in the former. Since no lipid stores were available in the *D* animals the efficient lipolytic activity required to sustain the endogenous triglycerides overproduction was impossible, and these findings indicate that hypertriglyceridemia in these animals is mainly caused by enhanced reductions in the use of circulating triglycerides by extrahepatic tissues. On the contrary, in the *D12-20* animals, where the lumbar fat pad weight remained at the same level as in *Controls*, their enhanced hypertriglyceridemia must be the result of a greatly augmented lipolytic activity which could be sustained by the normal fat stores they had accumulated during the first half of gestation, when they were not diabetics.

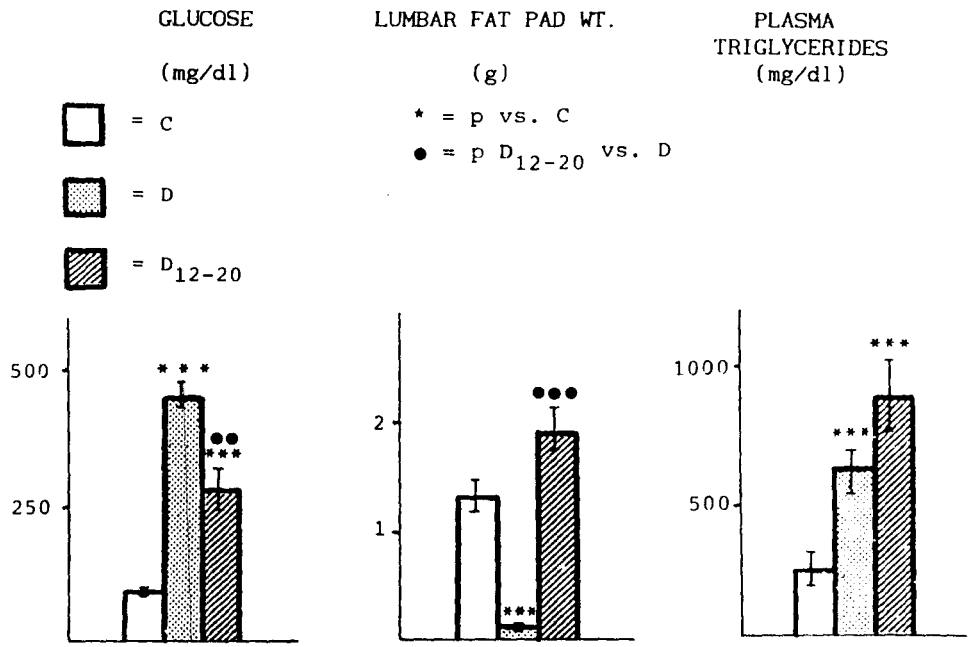

Fig. 5. Plasma glucose and triglyceride concentration and lumbar fat pad weight in 20 day-pregnant streptozotocin treated rats. Animals were intravenously treated with 45 mg/kg body weight of streptozotocin prior mating. One group was treated daily with subcutaneous replacent insulin therapy from the time of receiving the streptozotocin until sacrifice (*Controls*). Another group received the replacement insulin therapy only up to the 12th day of gestation, and therefore were maintained diabetic from that time until sacrifice (*D12-20*), and a third group that did not receive any therapy (*D*). Determinations of glucose and triglycerides were carried out as previously (4).

In summary, present findings indicate that maternal fat store accumulation during the first half of gestation has a pivotal importance on the development of maternal hypertriglyceridemia during late gestation. The question now is to discover what the role of these adaptations in the mother and fetus is.

CONSEQUENCES OF MATERNAL HYPERLIPIDEMIA

Increases in maternal circulating glycerol levels (30) caused by active lipolytic activity allow the use of this metabolite as a preferential gluconeogenetic substrate (31), and so contributes to the maintainance of sufficient glucose production for fetal and maternal tissues. Increments in circulating levels of triglycerides facilitate their use by the mammary glands prior to parturition, and this process is driven by the increased lipoprotein lipase activity found in this tissue at very late gestation (14,15). No other parts of the increase in circulating lipidic components in the fed mother during late gestation seem to directly benefit her metabolic needs. This increase, however, may benefit the fetus since this gestational period coincides with the rate of maximal fetal accretion, when the substrate, metabolic fuel, and essential component requirements of the fetus are greatly enhanced.

The lipid component may also constitute a circulating fuel store for both mother and fetus, which is easily accessible under conditions of food deprivation, and may explain the well-known finding of enhanced ketogenesis in the mother under fasting conditions (24,25,32,33). This hypothesis is sustained by the increased arrival of FFA in the liver as a result of greatly enhanced adipose tissue lipolysis (10, 11) and, by the increase in liver lipoprotein lipase activity recently published (4) which would facilitate maternal liver use of circulating triglycerides as ketogenic substrates.

The enhanced arrival of ketone bodies in fasted maternal tissues allows the ketone bodies to be used as metabolic fuels, and may spare other more limited and essential substrates, like 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.

TRANSFER OF LIPIDIC PRODUCTS TO THE FETUS

Having described the metabolic adaptations in the mother which cause her hyperlipidemic condition during late gestation, we shall review current bibliography treating the mechanism controling the placental transfer of FFA, glycerol and ketone bodies, the three maternal lipid metabolism products that most easily reach the fetus. Understanding the placental transfer process and respective metabolic fates of these products in the fetus should improve our grasp of the fetal consequences of rising lipid levels in maternal circulation.

Since the level of FFA, glycerol and ketone bodies in maternal circulation are a consequence of adipose tissue lipolytic activity, which is intensely enhanced in the starved late pregnant rat (10,30), the maternal/fetal ratio of these metabolites under this particular condition must be examined.

Table 2 summarizes the comparison of plasma levels in 48 h starved virgin rats and 19-day pregnant rats and their fetuses. It can be seen that whereas fetal FFA and glycerol levels are much lower than in the mothers, ketone bodies have a similar value. In an initial approach, these maternal/fetal concentration differences reflect the efficiency or magnitude of the placental transfer process.

Nutrient placental transfer may be accomplished by means of different mechanisms, such as facilitated diffusion, active transport and simple diffusion (35-38). Simple diffusion seems to be the common and unique mechanism for the lipidic-derived moieties, although some qualifications must be made. Simple diffusion is carried out from a region with a high concentration to one with a low concentration, and the rate of transfer is directly proportional to the concentration gradient and decreases with molecular size and hydrosolubility (39). Other factors can also specifically affect the efficiency of placental nutrient transfer (39-43): uterine and umbilical blood flows; the intrinsic placental metabolism (utilization versus production); and placental structure. The contribution of some factors which involve simple diffusion, like blood flow, is the same with any nutrient, but the contribution of other factors varies with each nutrient and must be considered specifically.

Free Fatty Acids

In addition to the essential fatty acids which support growth (44) and brain development (45) the fetus also needs the non-essential lipids from

Table 2. Circulating levels of FFA, glycerol and ketone bodies in 48 h starved virgin, and 19-day pregnant rats and their fetuses

	FFA (μM)	Glycerol (μM)	Ketone bodies (μM)
Virgin rats	443±21	153±10	982±67
Pregnant rats	739±59***	264±16***	2569±210***
Fetuses	45±12+++	36±13+++	2470±157
Maternal/ fetal ratio	16.6±0.8	7.0±0.5	1.02±0.08

Determinations were carried out as previously shown (4). Mean ± SEM of 6-8 rats/group. Statistical comparison of pregnant versus virgin rats: ***, $p<0.001$ and of fetuses vs. their mothers, +++, $p<0.001$. Not significant, $p>0.05$.

the mother. They are stored in fetal body fat, and become an important substrate during early post-natal life (46). Body fat at term can represent a substantial percentage of body weight (10% in the guinea pig and 16% in man) (47), and the fetus cannot synthesize enough fatty acids to satisfy these requirements. Using sheep (48) and rats (49), the initial studies on placental lipid transfer suggested that the amount of fatty acids transferred from the mother to the fetus was minimal, but subsequent investigations in species like the rabbit (50), the guinea-pig (51,52), the rat (54) and different primates (53), suggest that the transfer of fatty acids across the placenta can surpass the normal fetal lipid storage requirements (55).

Like other fats, fatty acids are insoluble in water and must be transported in the blood either as albumin-bound FFA, or else in their esterified form (triglycerides, phospholipids and esterified cholesterol) which associates with other lipids and proteins to form lipoproteins. Maternal FFA, esterified fatty acids that have been hydrolyzed at the placental level, and unmodified lipoproteins make up the potential sources for the fatty acids that reach the fetus.

Placental transfer of fatty acids varies considerably between different species. In general, fatty acid transfer is limited when the placental barrier is constitued by multiple maternal and fetal cell layers (sheep, pig and cat), whereas the net flux can be high when the placental barrier is only constituted by fetal layers (man, rabbit, rat and guinea-pig). The relative fatty acid concentrations entering the fetus from the placenta in these species reflect the circulating maternal free fatty acid concentrations with the common exception of arachidonic acid (56). Since a higher proportion of arachidonic acid has been found in fetal plasma than in maternal plasma in both ruminant (57) and non-ruminant species (58-61), it has been inferred that arachidonic acid synthesis by the placenta must contribute heavily to the fetal supply of this fatty acid (62-65).

Current evidence suggests that fatty acid transfer across the placenta is not selective and since essential and non-essential fatty acids use the same transfer mechanism, most investigators in maternal-fetal transfer experiments use ^{14}C-palmitic acid to represent all the fatty acids. The quantity of fatty acid transferred varies considerably between species

(66), but in all instances the transplacental non-esterified fatty acid gradient grossly regulates the system.

In vitro studies using perfused placenta and/or cultured trophoblast cells must be employed to study the mechanism of FFA transfer in the human placenta, and correlate FFA levels in maternal and umbilical blood. A more direct approach may be used with experimental animals to study the placental transfer of FFA. We infused (1-^{14}C)-palmitate tracer through the left uterine artery of 20-day pregnant rats for 20 min before comparing the amount of label in the placentas and fetuses from the left uterine horn with that found in the ones from the right horn (67) as we have done before with different substrates (68-71). While the left uterine horn received the tracer directly, it reached the right horn after dilution in the mother's circulation, and so the amount of substrate transferred to the fetus can be calculated as a function of the values for the maternal FFA concentration, the difference in radioactive levels in fetuses between the left and right uterine horns, and the left uterine blood flow. Results have been recently reported by us (72), and they may be summarized as follows: the estimated FFA transfer was significantly above zero, indicating that it is significant. Absolute value of FFA transfer appears to be higher than levels previously found for glycerol even though lower than those found for glucose or alanine (72).

Around 50% of the ^{14}C-lipids retained in the placentas after tracer infusion corresponded to esterified fatty acids, so a certain proportion of the FFA's reaching the placenta must have been esterified. Although the participation of fatty acid esterification in the FFA transfer process has not been ascertained as yet, an active placental capacity to form esterified fatty acids from maternal FFA has been described in man and other species (73-76). The presence of an active enzymatic glyceride hydrolytic system (phospholipase and triacylglycerol lipase), which would ensure rapid triglyceride and phospholipid turnover, indicates that the esterification/hydrolysis cycle in the placental cells is one type of placental FFA transport, as Szabo et al. (77) and Hummel et al. (78) already proposed.

Free fatty acid contribution by maternal circulating triglycerides in the rat (79,80), the rabbit (81), the guinea-pig (82,83) and man (84) have been demonstrated. However, the passage of intact triglyceride across the placenta has not been detected yet.

Lipoprotein lipase activity has been detected in the placentas of all the species studied (4,15,80,81,85,86). Placental triglyceride hydrolysis with a direct transfer of released non-esterified fatty acids to the fetus has been considered as a source for this activity, but direct studies with in situ perfused guinea-pig placenta have shown that this accounts for a very small percentage of all the fatty acid transferred to the fetus (83). Therefore, maternal triglyceride-rich lipoproteins that have been broken down in the placenta by lipoprotein lipase are of minor quantitative importance as a fetal source of fatty acids under normal conditions. However, under conditions of exaggerated maternal hypertriglyceridemia this system of fatty acid supply from esterified maternal fats in the presence of sustained placental lipoprotein lipase activity, become much more important as has been proposed in streptozotocin diabetic rats (80,87).

Glycerol

The active lipolytic activity of maternal adipose tissue causes persistent elevation of plasma glycerol levels during late gestation (30, 31). Although there are interspecies differences, the values for plasma glycerol concentration are generally higher than in the fetus (Table 2).

The maternal/fetal glycerol gradient is greater in those species with epitheliochorial placenta (ruminants) (88,89) than in those with a hemochorial placenta (90-92).

Few experimental studies of placental glycerol transfer have been made with any species. Although the low weight and uncharged molecule of glycerol facilitate placental transfer, the quantity of glycerol actually transferred is notably less than that of other metabolites with similar molecular characteristics such as glucose or L-alanine (71,93). In contrast with the carrier-mediated process followed by these two metabolites, placental glycerol transfer is carried out by simple diffusion (88,94).

The umbilical glycerol balance in sheep indicates that fetal uptake is very low, accounting for no more than 1.5% of all the total oxygen consumed by the fetus (89). Despite the very favorable gradient (90), transplacental glycerol transfer in man has been impossible to detect. When comparing different substrates, and by using an *in situ* placental infusion technique in the rat, we have found that the level of glycerol transfer is far below that the levels of transferred glucose and alanine (71). We have also found that the fetal-placental unit rapidly processes glycerol into lactate and lipids (91), and believe this rapid utilization may actively contribute to maintaining the consistently high glycerol gradient between maternal and fetal blood (33,90-93).

Accelerated turnover of maternal glycerol seems to be influenced by the high liver glycerolkinase activity which facilitates fast phosphorylation with subsequent conversion into glucose (30,31). Although this mechanism indirectly benefits the fetus by providing glucose from maternal adipose tissue breakdown product, it may limit the availability of sufficient extra glycerol molecules for transfer to the fetus. This hypothesis is supported by our earlier findings after hepatectomy and nephrectomy in pregnant rats where glucose synthesis was negligible and the maternal transfer of glycerol to the fetus was augmented (95).

Consequently, and besides the intrinsic mechanism, placental glycerol transfer seems to be limited by the effective and rapid maternal kidney cortex and liver utilization of this substrate in gluconeogenesis. Although the fetal-placental unit actively uses glycerol, helping to maintain a favorable transfer gradient, the quantitative and physiological role for glycerol in the fetus, except as a preferential substrate for fetal liver glyceride glycerol synthesis (91), seems to be limited under normal conditions. However, under conditions of exaggeratedly elevated maternal glycerol levels, the placental transfer of glycerol could become much more important as a substrate supply for the fetus, but this possibility has not been researched sufficiently.

Ketone Bodies

The plasma levels of ketone bodies during fasting in late pregnancy are greatly increased (24,25,32,96-100), and the same elevation occurs in pregnant diabetics even when they are not fasting (101,102). These conditions coincide with enhanced FFA arrival in the liver consequent to hightened adipose tissue lipolytic activity. Although some maternal tissues (for example: skeletal muscle) use them as alternative substrates under conditions of limited glucose availability secondary to hypoglycemia and/or reduced insulin levels or sensitivity, ketone bodies may easily cross the placental barrier for fetal use as energetic fuels and lipogenic substrates (103-107).

Placental permeability of any compound is affected not only by molecular size and lipid solubility but also by electrical charge. At the

physiological pH, 7.4, most of the two main ketone bodies, β-hydroxybutyrate and acetoacetate, would take dissociated or ionized form, which would retard their diffusion across the placenta to the fetus. In spite of this, man (91,99,108-110), rat (24,32,111) and sheep (98,112), all species studied, rising maternal ketone bodies are followed by rising fetal plasma levels, indicating efficient placental transfer since fetal liver ketogenesis is practically negligible (113).

Although ketone body transfer through the placenta is performed by simple diffusion, it has a high unspecific component (88), and its efficiency varies with species. Whereas the maternal-fetal gradient for ketone bodies is above 10 in the sheep (98,112), in man it is about 2 (91), and in the rat it is close to 1 (24,33,111) (Table 2), indicating that the amount of ketone bodies transported to the fetus is much higher in non-ruminant than in ruminant species. These interspecies differences also affect the particular fetal ketone body oxidative metabolism since in the case of sheep, the ketone body oxidative metabolism account for no more than 3% of the total fetal oxygen consumption (98,114), whereas in fetal rat brain and liver it has been shown that β-hydroxybutyrate can adequately replace the glucose deficit during fasting hypoglycemia (104). This suggests that ketone bodies are much more important for the oxidative metabolism in non-ruminant fetuses under fasting conditions than they are for ruminants.

The enzymes 3-hydroxybutyrate dehydrogenase (E.C. 1.1.1.30), 3-oxoacid-CoA transferase (E.C. 2.8.3.5) and acetyl-CoA acetyltransferase (E.C. 2.3.1.9), which are the key ones to ketone body utilization, have been found in brain and other tissues of both human and rat fetuses (105,115-117). *In vitro* β-hydoxybutyrate oxidation in the human and rat brain depends on substrate concentration rather than maternal nutritional state (103, 104, 107). Fetal kidney, heart, liver and placenta have been demonstrated to oxidize ketone bodies (105, 118), and some have used ketone bodies as substrates for fatty acid and cholesterol synthesis, as has been shown in *in vivo* experiments in the rat brain, liver, placenta and lung after ^{14}C-β-hydroxybutyrate administration to pregnant animals (119). Starvation during the last days of gestation (120), or high fat feeding (117), create maternal hyperketonemia which rises ketone-body metabolism enzyme activity in fetal tissues and protects the fetal metabolic economy by the preferential use of ketone bodies as both oxidative fuels and carbon donors in the anabolic processes.

The maternal ketone bodies that cross the placenta are used by the fetus in non-ruminant species as preferential substrates for both oxidation and lipogenesis, thereby allowing the other substrates (glucose, lactate and amino acids) to be consumed in different pathways. Since both placental transfer and utilization of ketone bodies are concentration dependent, the quantitative contribution of these lipidic products to the fetal metabolism is significant only under conditions (starvation, high fat diet, diabetes, ...) that produce maternal hyperketonemia.

SUMMARY AND FINAL REMARKS

Maternal body fat accumulation during the first part of gestation is mainly sustained by hyperphagia and enhanced lipogenesis. This condition is of pivotal importance in the maintenance of the metabolic adaptations that take place during late gestation. Provoking hypothyroidism or diabetes in pregnant rats during the first 12 days of gestation only, blocks fat accumulation, hinders maternal hypertriglyceridemia and catabolic responses during the second gestational phase and impairs normal fetal growth.

Increased adipose tissue lipolysis, reduced uptake of circulating

triglycerides secondary to decreased adipose tissue lipoprotein lipase activity, hepatic overproduction of triglycerides and enhanced absorption of dietary lipids result in the maternal circulating triglycerides rise found during late gestation.

Besides fulfilling her own metabolic needs, sustained maternal hyperlipidemia during late pregnancy is very important for fetal development. Placentally transferred free fatty acids are directly needed by the fetus to sustain the continuous growth of its structures and accumulate circulating lipids and the fat depot. The fetus also benefits from the two other products of maternal lipid metabolism that we have considered: glycerol and ketone bodies.

Placental transfer of maternal glycerol is quantitatively small, but it is used by the fetal liver for the fatty acid esterification and actively contributes to the fetal triglyceride synthesis. The fetus mainly benefits from maternal hyperglycerolemia in a secondary manner. Glycerol is a preferential substrate for maternal gluconeogenesis, and since the fetal oxidative metabolism is fuelled principally by maternal glucose crossing the placenta, the use of this maternal adipose tissue lipolysis product for glucose synthesis actively contributes to fetal glucose supply.

Maternal ketone bodies easily cross the placenta and are efficiently used as either carbon fuels for the oxidative metabolism or as lipogenic substrates by the fetus, specially in non-ruminant species. Since all these processes are concentration-dependent, they do not become relevant unless conditions of maternal hyperketonemia exist. Under healthy physiological conditions they constitute an important support for the fetal metabolism when the availability of other substrates is more limited as is the case during periods of maternal starvation. In this situation brain development seems to be specially preserved as a result of the capacity of the fetus to use these metabolites.

Maternal hypertriglyceridemia during late gestation is also important as preparation for lactation. The level of circulating triglyceride-rich lipoproteins is not as high as would be expected, or may even decline, because of their augmented removal by the mammary gland for milk synthesis.

We may therefore conclude that although placental transfer of lipidic products has normally been undervalued, sustained maternal hyperlipidemia during late pregnancy is of pivotal importance for the offspring not only during their intrauterine life but also during suckling. This hyperlipidemia is, however the result of several dynamic and intrincate metabolic adaptations, and any deviation in them may directly modify the maternal lipoprotein profile and under pathological conditions the alteration may be permanent.

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