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MATERNAL-FETAL METABOLIC RELATIONSHIP

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INTRODUCTION

Although in a general context pregnancy may be considered a physiologic event wherein the intermittently feeding mother must provide a continuous supply of nutrients to the steadily growing fetus, there are at least two clearly differentiated metabolic conditions. During the first two thirds of gestation, coinciding with a minimal weight accretion by the conceptus, the mother conserves more exogenous nutrients whenever she eats, and this, together with her hyperphagia[1,2], results in an increase in the weight of her own structures (figure 1) which is specially manifest in her accumulation of fat depots. In the later part of gestation, rapid fetal growth (figure 1) is sustained by the intense transfer of nutrients from maternal circulation. This causes a switch to a net catabolic state which is specially evident in adipose tissue[3,4] and must be responsible for the decline in the conceptus-free maternal body weight (figure 1). These conditions become specially manifest when food is withheld and the catabolic response becomes heightened[5]. Under this condition exaggerated ketogenesis and gluconeogenesis contribute to the availability of fuels to the fetus which is partially preserved from maternal metabolic insult. As shown in figure 2, 24 h of starvation produced a greater body weight loss in 21 day pregnant rats than in age matched nonpregnant female controls, whereas fetal body weight was unchanged. It is, however, known that more prolonged starvation slows the fetal growth rate[6] although there are organs such as the brain that are better preserved than others.

This chapter reviews the carbohydrate-lipidic interactions that occur during pregnancy and some of their metabolic consequences such as the development of maternal hypertriglyceridemia.

CARBOHYDRATE METABOLISM DURING PREGNANCY

After short or prolonged fasting periods, maternal hypoglycemia develops during late gestation[7-9]. Since glycogen stores are depleted under this fasting condition the hypoglycemia may be the result of decreased gluconeogenesis, an enhanced rate of glucose utilization or both.

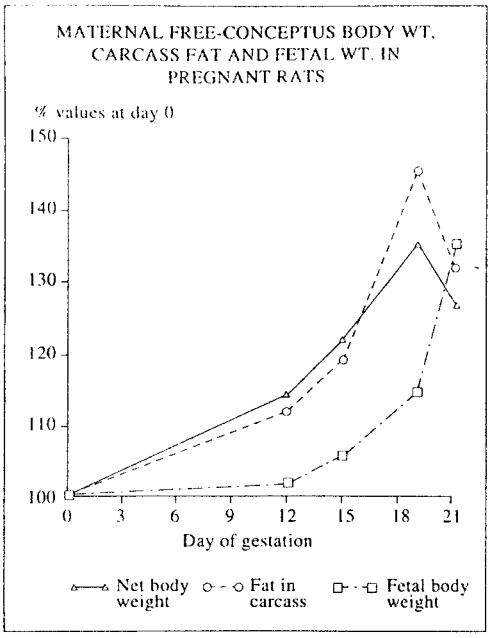

Figure 1. *Change of conceptus free maternal body weight and of carcass fat content expressed as percentage of values at day 0, and of fetus body weight in the pregnant rat. The latter parameter is expressed as (absolute values x 10)+100.*

The circulating level of gluconeogenic substrates fluctuates during fasting in late pregnancy. As shown in figure 3, whereas in the pregnant fasted rat plasma levels of lactate or pyruvate are kept similar to those in virgin controls, gluconeogenic amino acids are decreased and glycerol levels are increased. However, we have found that after the *in vivo* administration of either a tracer or substrate amounts of labelled pyruvate or glycerol, their conversion into glucose in the fasted pregnant rat is always greater than in virgin controls[9-12]. When the administered tracer is small amounts of alanine (0.2 mmols) the synthesis of glucose was the same in pregnant as in virgin animals whereas when given in larger amounts (1 mmol) glucose synthesis appreared higher in pregnant than in virgin animals[10]. This finding indicates that the larger amount of tracer may have compensated for the differences of endogenous alanine levels overcoming their potentially limited use as an efficient gluconeogenic substrate in the pregnant rat.

It may then be concluded that although gluconeogenesis from those three carbon substrates is enhanced in the late pregnant fasted rat, alanine, and probably other gluconeogenic amino acids as well, are not used as a preferential substrate in this pathway because of their reduced availability. Placental transfer of amino acids is carried out through an active transport system which results in their concentration in fetal plasma being even higher than in maternal plasma[13-15]. The presence of the conceptus therefore interferes with the maternal glucose-alanine cycle between the liver and the skeletal muscle[16].

Another conclusion that may be reached from the above "in vivo" gluconeogenetic experiments in the late pregnant rat is that glycerol is one of the most efficient substrates in its conversion into glucose. This conclusion is not surprising since, unlike most other substrates, the pathway of glycerol up to glucose does not require intramitochondrial steps (figure 4) which, together with the high glycerokinase activity in liver and kidney cortex[17], allow this metabolite to be rapidly converted into glucose[10], thus becoming an efficient gluconeogenic substrate in pregnancy under both fed and fasting conditions[10,18,19].

Since reduced gluconegenic activity can not be claimed to justify maternal tendencies to hypoglycemia, these tendencies must be the result of enhanced glucose utilization. The rates of glucose utilization in several species have al-

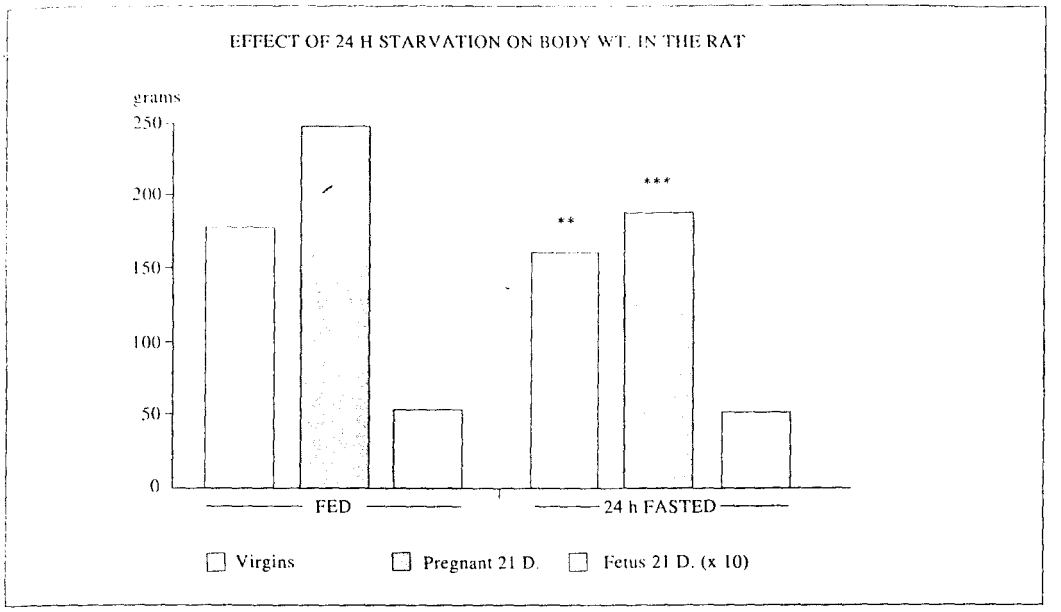

Figure 2. *Effect of 24 h starvation on body weight in virgin and 21 day pregnant rats and their fetuses. Asterisks correspond to the statistical comparison between fed and 24 h fasted rats.*

ways been found to be higher in pregnant than in nonpregnant females[20]. This effect specifically corresponds to glucose utilization by the conceptus since glucose utilization by maternal tissues is lower than in nonpregnant animals[20,21] whereas glucose utilization by the conceptus may represent up to 50% of overall maternal glucose utilization[21-24].

The importance of the fetal consumption of maternal metabolites may be inferred from the quality and quantity of their placental transfer. As shown in figure 5, obtained from our previous studies on the maternal-fetal transfer of a variety of substrates in the late pregnant rat *in situ*[15,25,26], glucose transfer is much higher than the transfer of alanine, palmitic acid, glycerol and triglycerides. This preponderance of placental glucose transfer is justified because despite the fact that under normal conditions the fetus cannot synthesize glucose, this matebolite is a major fuel in its metabolic economy[27].

ADIPOSE TISSUE METABOLISM

Lipolytic activity

Because the adrenal medulla is selectively activated by reductions in blood sugar[28,29], maternal hypoglycemia under mild dietary deprivation seems to be responsible for the increase in catecholamine excretion found during late gestation in the fasting rat[30,31]. This increased sympatho-adrenal activity together with the enhanced gestational hormones released by the placenta and ovary may be responsible for the accelerated mobilization of the fat depot that occurs during late gestation under both fed and fasting conditions[32-34].

Enhanced adipose tissue lipolysis incre-

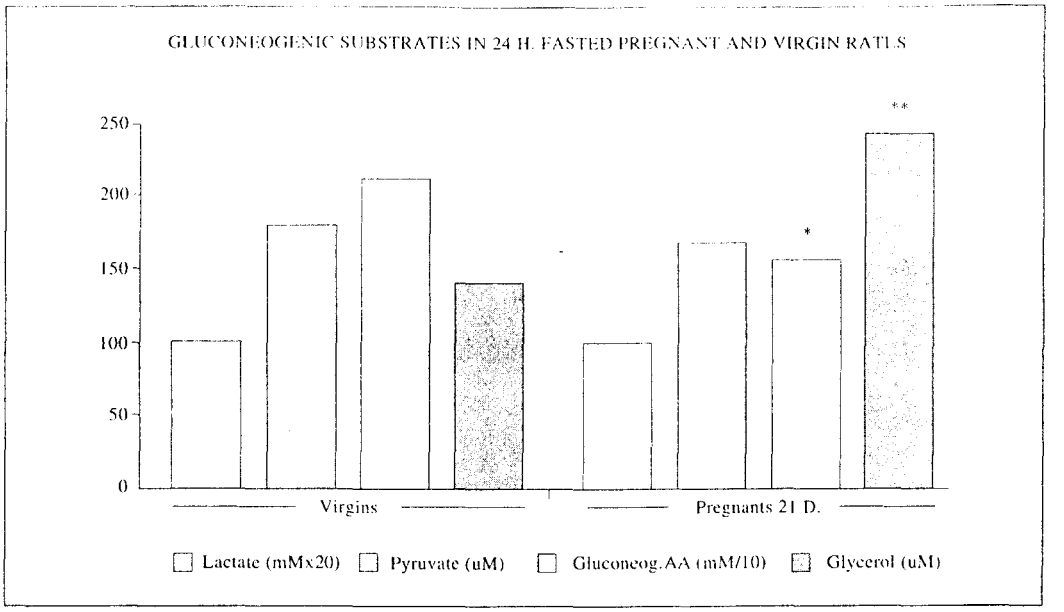

Figure 3. *Plasma level of gluconeogenic substrates in 24 h fasted 21 day pregnant rats. Gluconeog. AA= Gluconeogenic amino acids (Ala, Glu, Gln, Asp, Asn, Ser, Gly, and Thr). Asterisks correspond to the statistical comparison between pregnant and virgin rats. Methodological details as described in ref. 12.*

ases the release of both free fatty acids (FFA) and glycerol into maternal circulation where they reach high plasmatic values[5,6,32]. As shown in figure 5, the placental transfer of these two lipolytic products is low[35,36] whereas the maternal liver is their main receptor[37,38]. As shown in figure 4, in the liver, after being converted into their respective active forms (FFA to acyl- CoA and glycerol to α-glycerol-phosphate) they may be used for esterification in the synthesis of glycerides. Other pathways used for these compounds are: ß-oxidation to acetyl-CoA and ketone body production in the case of FFA, and glucose synthesis in the case of glycerol. We have indicated above that glycerol is used as a preferential gluconeogenic substrate in gestation and we have previously shown that the use of glycerol for glyceride glycerol synthesis is also very efficient in the liver of the fed 21 day pregnant rat[19].

As will be commented below, liver production of triglycerides is enhanced during late pregnancy[39-41], a change that, among other factors, is supported by the augmented transmission of FFA and glycerol to the liver from adipose tissue lipolysis and the active esterification activity in the liver.

Under fed conditions, the fetus does not directly benefit from these changes since maternal triglycerides do not directly cross the placental barrier (see figure 5). However, in the fasting condition the use of both FFA for ketogenesis[42,43] and glycerol for gluconeogenesis[10] is greatly enhanced in the liver of the pregnant mother. Ketone bodies freely cross the placenta[36] and may be

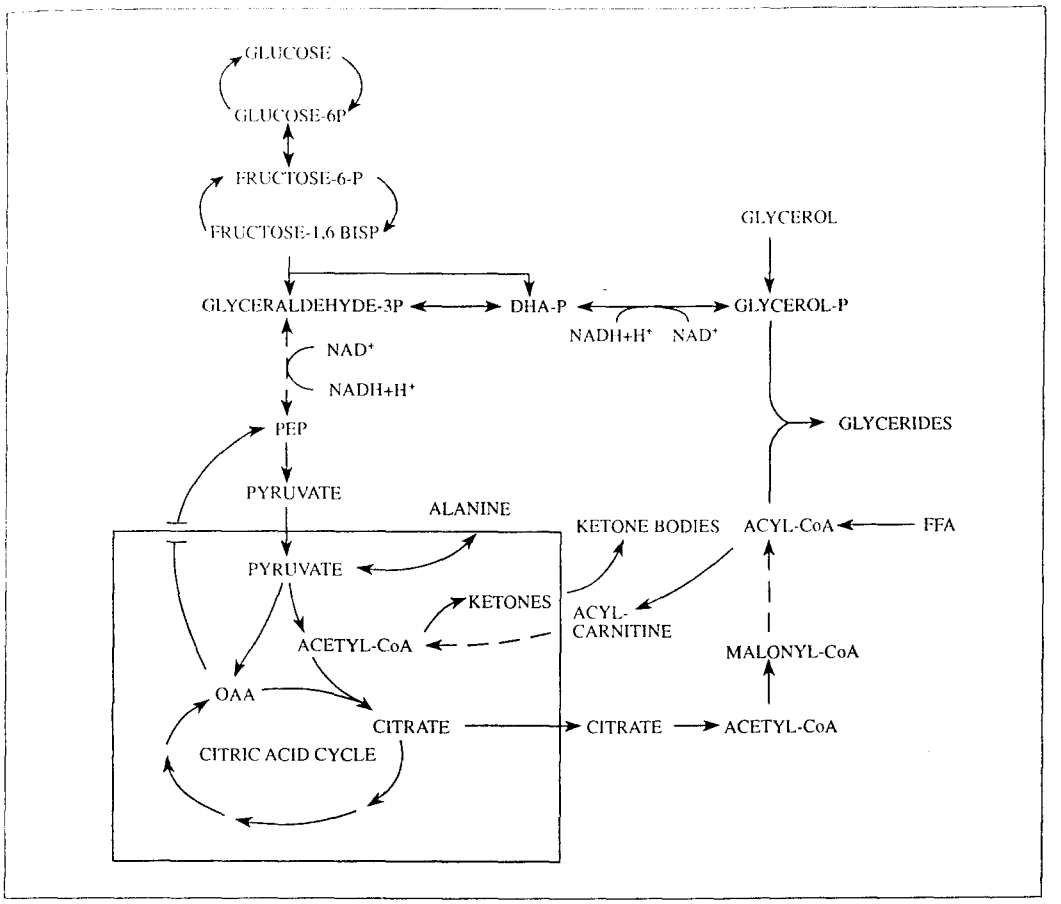

Figure 4. *Metabolic interactions between gluconeogenesis (glucose synthesis), glycolysis (glucose conversion into pyruvate), citric acid cycle and metabolism of FFA and glycerol in the liver.*

used as fetal fuels[6,44-46] or even as substrates in brain lipid synthesis[47]. Increased glycerol levels in maternal circulation together with both the preferential use of this metabolite as a gluconeogenic substrate and the efficient transfer of glucose to the fetus commented above also benefit the fetus under conditions of reduced availability of other substrates such as amino acids[10,42].

The active adipose tissue lipolytic activity in the mother therefore plays a critical role in the fetus, specially under fasting conditions. It also benefits maternal tissues since the lipolytic products, and very specialy FFA and ketone bodies, may be used as alternative fuels to spare glucose.

Fat accumulation

Sufficient maternal fat depots are necesary to sustain her accelerated adipose lipolytic activity. Accumulation of body fat is one of the most striking features of gestation in both women[48,49] and experimental animals[50-53]. As shown in fi-

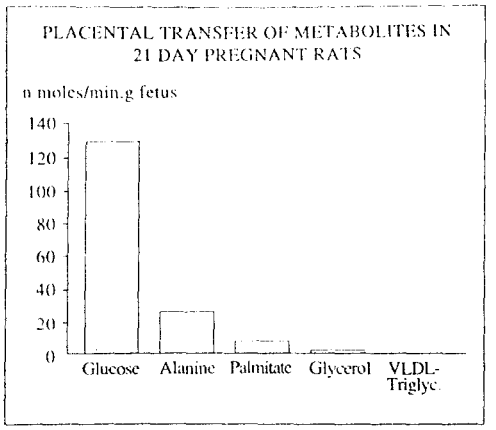

Figure 5. *Placental transfer of metabolites in 21-day pregnant rat measured in situ as function of the radioactivity that appeared in fetuses after infusing the respective labeled tracer through the left uterine artery and making proper corrections of the data for specific activity dilution of the tracer and uterine blood flow as described elsewhere*[15,25].

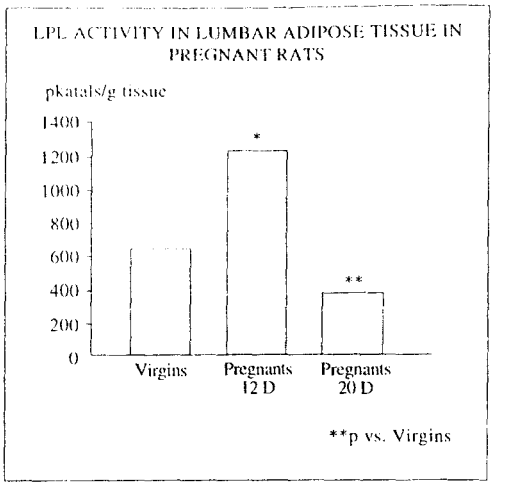

Figure 6. *Lipoprotein lipase activity in lumbar adipose tissue of 12- and 20-day pregnant rats and their virgin controls. Methodological details as previously described*[61,63]. *Asterisks correspond to the statistical comparison between pregnant and virgin rats.*

gure 1, corresponding to the pregnant rat, body fat accumulation accounts for most of the conceptus free maternal body weight increase. Body weight increases progressively during gestation but stops or even declines during the last third of pregnancy, coinciding with the phase of maximal lipolytic activity.

Fat accumulation during the two first thirds of gestation may be associated with three major changes: hyperphagia, enhanced lipogenesis and increased lipoprotein lipase activity. From studies in the rat it is known that hyperphagia supervenes shortly after mating and increases as gestation time advances[1,2]. This change enhances the availability of exogenous substrates and must contribute to the maternal accumulation of fat depots since it is not found under conditions of food restriction[50,52,54,55]).

Glucose is quantitatively the most efficient substrate to be converted into lipids by adipose tissue[56]. Glucose utilization for fatty acids and glyceride glycerol synthesis by periuterine adipose tissue *in situ* in pregnant rats was estimated at different days of gestation[57]. It was found that both lipogenesis (fatty acid synthesis) and glycerolgenesis (glyceride glycerol synthesis) increased until day 20 and then decreased sharply on day 21. This active lipid synthesis must therefore also contribute to the fat accumulation occurring during the two first trimesters of gestation.

Lipoprotein lipase is an enzyme which controls the so called "fat uptake" in adipose tissue. It is located at the capillary endothelium where hydrolyses the triglycerides circulating in plasma in the form of triglyceride-rich lipoproteins and facilitates the uptake of the hydrolytic products, FFA and glycerol, by the subjacent tissue[58]. As shown in

figure 6, the lipoprotein lipase activity in lumbar fat pads is higher at day 12 of gestation in the rat than in nonpregnant animals (day 0). It may then be suggested that at this time of gestation maternal adipose tissue actively hydrolyses and takes up circulating triglycerides and that this action may also contribute to the accumulation of body fat occurring during the first part of gestation.

As also shown in figure 6, lipoprotein lipase activity in adipose tissue decreases at day 20 of gestation in the rat, which confirms previous findings[59-61]. This effect, together with the reduction in fatty acids and in glyceride glycerol synthesis and the increased lipolytic activity commented above, results in the net increase in fat depot breakdown that occurs before parturition. The benefits of this striking transition from an anabolic to a catabolic condition in the maternal lipid metabolism are not yet understood completely because, although this transition coincides with the maximal fetal growth phase ([53] and figure 1), lipids can only cross the placental barrier with difficulty ([36,62] and figure 5). As will be commented below, this condition allows maximal development of maternal hypertriglyceridemia which, together with the presence of lipoprotein lipase activity in the placenta[61,63] and in the mammary gland[61,63], may warrant the access of essential fatty acids to the fetus and the newborn.

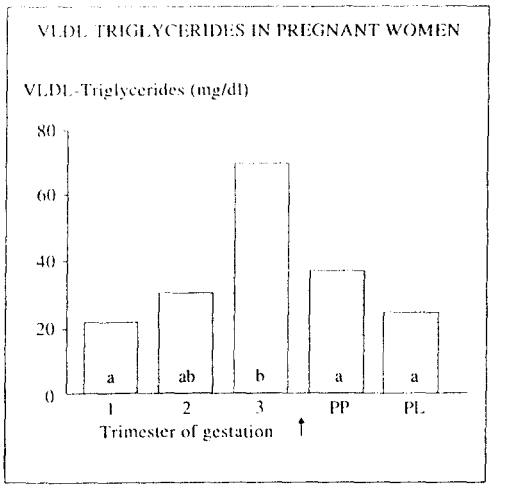

Figure 7. *VLDL-triglycerides concentration in plasma during the three trimesters of gestation, 2-4 weeks postpartum (PP) and at postlactation (PL) in women. Methodological details as previously described[63]. Statistically significant difference between two groups is indicated by different letters whithin the respective bars.*

MATERNAL HYPER TRIGLYCERIDEMIA

Hypertriglyceridemia is a common feature in normal pregnancy both in women[63-66] and in the rat[67,68]. Although from a longitudinal study in pregnant women at different stages of gestation we know that it corresponds to an enrichement of triglycerides in all circulating lipoproteins[69], quantitatively, the greatest change is found in the plasma VLDL-triglyceride levels. These lipoproteins are synthesized in the liver and the triglycerides that carry them must procede either from the fatty acids and glycerol that are synthesized within this organ or from those that reach it from circulation. As shown in figure 7, the plasma concentration of VLDL-triglycerides progressively increases with gestational time in pregnant women, attaining the highest value at the 3rd trimester and declining rapidly after parturition.

Multiple factors may contribute to such an increase in VLDL-triglycerides. One of them must be the active adipose tissue breakdowm which is especially intense during late gestation. The enhanced arrival of the lipolytic products,

FFA and glycerol, to the liver would facilitate their use for triglyceride synthesis and the export of triglycerides to the circulation in the form of VLDL. An enhanced production of VLDL-triglycerides has been directly demonstrated in perfused liver from pregnant rats[70], and the same conclusion has been reached from indirect experiments[39]. The progressive and intense increment of estrogens occurring during gestation may be responsible for the enhanced liver VLDL production[71].

Another factor that may contribute to the increment of VLDL-triglycerides in maternal circulation is the reduction in adipose tissue lipoprotein lipase activity commented above. Since this enzyme controls the catabolism of the VLDL-triglycerides, this change could be compensated for a change in the opposite direction in the activity of this enzyme in other tissues, as has been found to occur in heart, placenta, and, very specially, in mammary gland[61]. However, when measuring post-heparin lipoprotein lipase activity as an index of the overall activity of this enzyme in the whole body in pregnant women, we have recently found that it is decreased at the 3rd trimester of gestation as compared to earlier stages of gestation and post-partum, indicating that such a change may, at least in part, impede a normal catabolic rate in the exaggerated amount of VLDL-triglycerides that are present in the mother during the last gestational trimester. Here again, this change in tissue lipoprotein lipase activity that occurs during late gestation seems to be driven by hormonal factors, and whereas the decrease in adipose tissue enzyme activity is caused by maternal insulin resistance[72], the increase in mammary gland is known to be induced by the increment in plasma prolactin levels occurring before parturition[61].

Besides being a floating energy source for rapid use under emergency conditions such as starvation, where circulating triglycerides may be used as substrates for liver ketogenesis[63], the major physiological role of maternal hypertriglyceridemia is its active contribution to milk synthesis in preparation of lactation. We have previously shown that following an oral load of labelled triglyceride there is a rapid appearance of labelled lipids in mammary gland[73] and that blocking the increase in mammary gland lipoprotein lipase activity by tratment with progesterone in the late pregnant rat, completly inhibits the decline in plasma triglycerides normally occurring around parturition in the rat[61]. These findings demonstrate that the rapid and intense increase in mammary gland lipoprotein lipase activity before parturition facilitates the clearance of circulating triglycerides and their use in milk synthesis.

SUMMARY

During the first two thirds of gestation, coinciding with a minimal accretion by the conceptus, the mother is in an anabolic state which is supported by her hyperphagia and the more efficient conservation of exogenous nutrients whenever she eats. During this phase maternal fat depots are accumulated thanks to the enhancement in adipose tissue lipogenic and glycerolgenic activity. In the latter part of gestation, on the contrary, the rapid fetal growth is sustained by the intense transfer of nutrients from maternal circulation. Glucose is quantitatively the most abundant of the different substrates that cross the placenta and despite enhanced maternal gluconeogenesis this transfer is the cause of the maternal tendency to hypoglucemia. This causes a switch to a net catabolic state which is

specially evident in the net breakdown of fat depots. Enhanced release of adipose tissue lipolytic products, FFA and glycerol, facilitates the liver synthesis of triglycerides and their later release into circulation associated to VLDL. Glycerol is also used as an important gluconeogenic substrate and FFAs are broken down through ß-oxidation for ketone body synthesis. These pathways become heightened when food is withheld and actively contribute to the availability of fuels to the fetus which becomes partially preserved from maternal metabolic insult. Enhanced liver production of VLDL triglycerides and decreased extrahepatic lipoprotein lipase contribute to exaggerated maternal hypertriglyceridemia which, besides being a floating metabolic reserve for emergency conditions such as starvation, constitutes an essential substrate for milk synthesis around parturition in preparation for lactation.

Key words: Pregnancy, Adipose tissue, Glucogenesis, Lipoproteins, Hypertriglyceridemia.

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