In: "Maternal and Extrauterine Nutritional Factors. Their Influence on Fetal and Infant Growth". F. Battaglia, F. Falkner, C. Garza, B. Salle et al., eds. Ediciones Ergon, S.A., Madrid 1996, pp. 115-126.

LIPID METABOLISM DURING GESTATION AND ITS IMPLICATIONS FOR INTRAUTERINE DEVELOPMENT

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ABSTRACT

Although lipids do not easily cross the placenta they have important implications in fetal development. Adipose tissue lipolytic activity is enhanced during late gestation, and the release of glycerol and free fatty acids facilitates their increased availability in the liver where they are used in the synthesis of triglycerides, or are respectively converted into glucose or ketone bodies. During late pregnancy there is a preferential use of glycerol for gluconeogenesis, which, together with the efficient transfer of glucose throughout the placenta assures the availability of this essential fuel to the fetus. Under fasting conditions maternal ketogenesis is greatly enhanced and, since ketone bodies freely cross the placenta and are used by the fetus as fuels and lipogenic substrates, they actively contribute to fetal development. Maternal body fat accumulation takes place during the first two thirds of gestation, is mainly supported by hyperphagia and increased lipogenesis, and is essential for the catabolic condition present during the last third of gestation. Conditions like hypothyroidism that impede the building of fat depots have negative consequences not only for maternal metabolism but also in fetal development. Maternal hyperlipidemia consists primarily of an increase in triglycerides in all the circulating lipoproteins with smaller increments in cholesterol. The greatest change corresponds to an increment in VLDL-triglycerides, which is the result of multiple factors, although the main one is their enhanced production by the liver. The benefit that maternal hypertriglyceridemia has for the fetus and newborn is multiple, in spite of the fact that triglycerides do not cross the placenta: 1) Under fasting conditions, circulating triglycerides are driven to the liver where the increment of lipoprotein lipase activity (LPL) from extrahepatic sources allows their use for ketone body synthesis. The ketone bodies are released into the circulation, easily cross the placenta and used by the fetus; 2) The presence of LPL in the placenta allows essential dietary fatty acids carried as triglycerides in maternal plasma to become available to the fetus, and 3) The induction of LPL activity in the mammary gland around parturition drives maternal plasma triglycerides to this organ allowing essential fatty acids of dietary origin to become available to the suckling newborn.

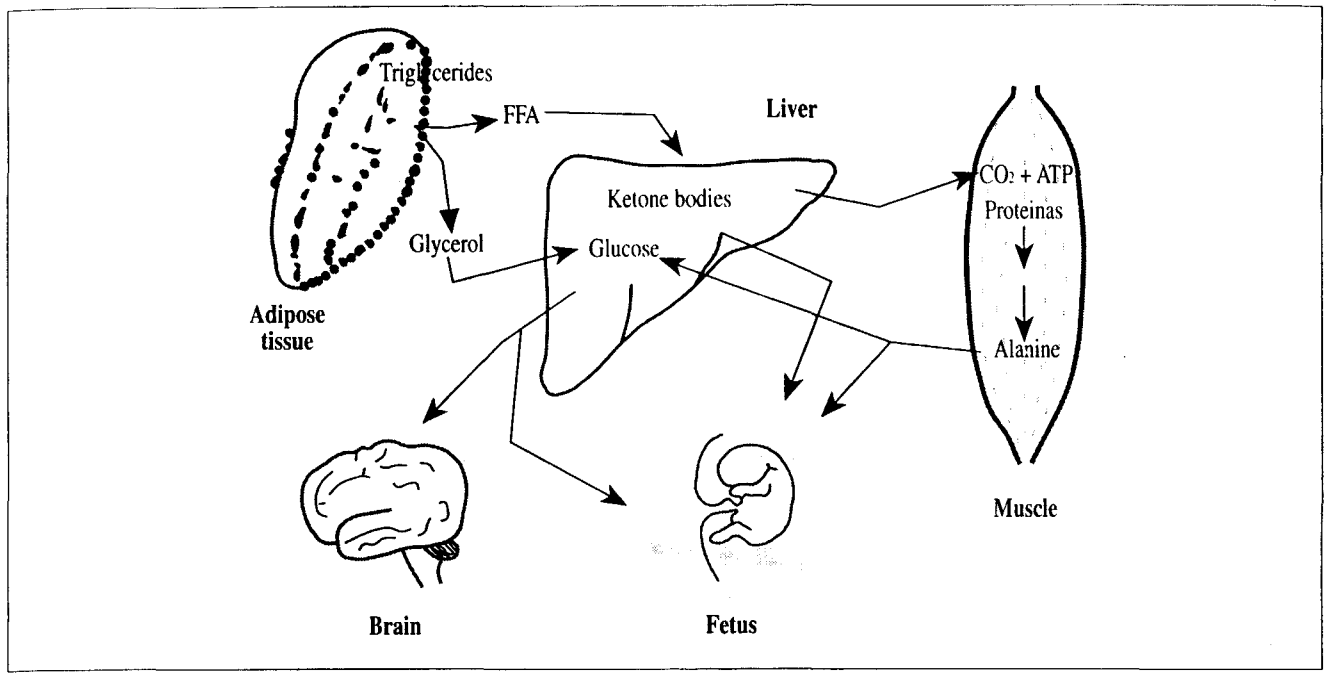

Figure 2. *Metabolic response to starvation at late pregnancy showing the role of adipose tissue as a source of substrates for the liver synthesis of both glucose and ketone bodies, and the availability of these compounds to maternal and fetal tissues.*

The comparative in vivo conversion of equimolecular amounts of three labelled gluconeogenic substrates, ^{14}C-pyruvate, ^{14}C-alanine and ^{14}C-glycerol into circulating glucose when given to 24-h fasted pregnant rats or virgin controls shows a higher gluconeogenic activity in the pregnant rat than in virgin animals, glycerol being the most efficient substrate converted into glucose[8,32,33]. This finding, together with the fact that, as shown in Figure 1, glycerol is the only gluconeogenic substrate which plasma level appear higher in fasted 20 day pregnant rat than in fasted virgin animals, means that glycerol reaching the liver from adipose tissue lipolytic activity is used as a preferential gluconeogenic substrate during late pregnancy. The enhanced use of glycerol as an efficient gluconeogenic substrate in pregnancy is even seen in fed conditions where the use of other substrates is, however, unchanged[33,34].

The use of FFA for ketone body synthesis does not seem to be enhanced in late gestating rats under fed conditions, where plasma ketone bodies concentrations are even lower in pregnant than in virgin rats[35]. However, under fasting conditions, the use of FFA for ketogenesis is greatly enhanced in the liver of the pregnant mother[35,36].

As summarized in Figure 2, these two changes occurring during late pregnancy under fasting conditions secondary to the active adipose tissue lipolytic activity, enhanced gluconeogenesis from glycerol and ketogenesis from FFA, may benefit the fetus which, at this late phase of gestation is at its maximum accretion rate and whose requirements for substrates, metabolic fuels, and essential components are therefore greatly enhanced. The preferential use of glycerol as a gluconeogenic substrate and the efficient transfer of the newformed glucose to the fetus, thus, is of pivotal importance to the fetus under these fasting conditions of reduced availability of other substrates such as amino acids[8,33,37]. The enhanced gluconeonenic activity during late pregnancy under fasting conditions is also essential for certain maternal tissues like the brain which continuously needs

periuterine adipose tissue in situ at different days of gestation in the pregnant rat[46]. It was found that both the synthesis of fatty acids and of glyceride glycerol from glucose progressively increased until day 20 of gestation, to sharply decline on day 21. An enhanced fatty acid synthesis in pregnant rats was also found when studied in vivo[47], and this active lipid synthesis seems to be the main factor contributing to the fat accumulation occurring during the first two trimesters of gestation.

An additional possibility that has been proposed as responsible for the fat accumulation during the early phases of gestation is an increase in the lipoprotein lipase (LPL) activity in adipose tissue. This enzyme is normally bound in its active form to the capillary endothelium of extrahepatic tissues and hydrolyses the triglycerides circulating in plasma in the form of triglyceride-rich lipoproteins, VLDL and chylomicrons, which are respectivelly converted into intermediate density lipoproteins (IDL) and remnant particles (Fig. 3)[48-50]. The products of this triglyceride hydrolysis, FFA and glycerol, are partially taken up by the subjacent tissue[51], and therefore, this enzyme controls the fat uptake in adipose tissue. Although few reports, including our own, show that at day 12 of gestation in the rat there is an increase in adipose tissue LPL activity[37,43], the change is small and not always reproduced[52]. We must therefore conclude that an enhanced adipose tissue LPL activity does not contribute to the accumulation of body fat occurring during the first part of gestation.

Different to the small change found during early gestation, LPL activity in adipose tissue intensely decreases during late gestation in the rat[11,52-55], and in women a significant reduction in the post-heparin LPL activity has also been reported to appear at the third trimester of gestation[56,57]. This change indicates a reduction in fat uptake by adipose

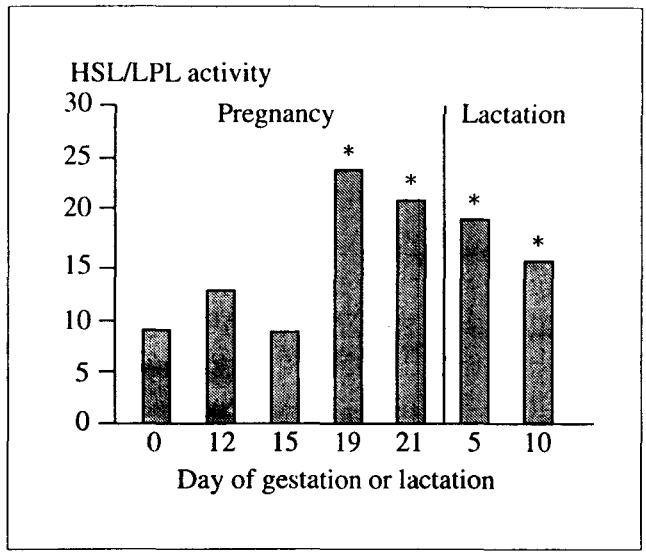

Figure 4. *Ratio of hormone sensitive lipase (HSL) and lipoprotein lipase (LPL) activities in lumbar adipose tissue at different days of gestation and lactation in the rat. Asterisks correspond to the statistical comparison with values in virgin rats (day 0) (*= $p<0.05$). Adapted from ref. 52.*

tissue during late gestation, which together with the increased lipolytic activity commented above, results in an accelerated breakdown of fat depots during the last third of gestation. These changes are clearly seen when the ratio of the activities of the two key enzymes controling lipolysis (hormone sensitive lipase, HSL) and fat uptake (LPL) in adipose tissue is considered. As shown in Figure 4, whereas the ratio of HSL to LPL activities is kept low and stable in virgin and 12 and 15 day pregnant rats, it greatly increases at day 19 of gestation, remaining increased during the lactating phase. This transition from an anabolic to a catabolic condition in the maternal lipid metabolism coincides with the maximal fetal growth phase[11,28,41] and therefore, when the mother needs not only to sustain but progressively increase the supply of nutrients to the fetus. As will be discussed below, this situation permits maximal development of maternal hypertriglyceridemia and an accelerated responsiveness to starvation. This allows spare glucose and other essential metabolites (such as amino acids), to be therefore of essential importance not only to the maternal metabolic economy but to fetal development.

exaggerated increase in VLDL-triglycerides during gestation. The enhanced lipolytic activity in adipose tissue commented above facilitates the greater arrival of both FFA and glycerol to the liver, enhancing their use for triglyceride synthesis and their subsequent release into circulation in the form of VLDL. An increased liver production of VLDL-triglycerides has been demonstrated in pregnant rats[64,65].

Another factor that may contribute to the increment of VLDL-triglycerides in maternal circulation is the reduction in adipose tissue LPL activity which is consistently seen during late gestation. As commented on above, this enzyme controls the catabolism of VLDL-triglycerides (see Figure 3). A reduction of LPL activity in adipose tissue could be compensated for by a change in the opposite direction in other tissues, as was shown to occur in pregnant rats in the heart, the placenta, and, especially, in mammary gland[11,55]. However, when measuring post-heparin LPL activity as an index of the overall activity of this enzyme in the whole body in pregnant women, we found that it is decreased during the 3rd trimester of gestation as compared to earlier stages of gestation and post-partum[57,66]. This change suggests that during late gestation the overall reduction of LPL activity in maternal tissues must impede the normal catabolic rate of the VLDL-triglycerides present in maternal circulation, contributing to their exaggerated increase.

Besides its physiological implications for both the mother and the fetus, the abundance of VLDL-triglycerides in the mother's plasma during late gestation affects the normal lipidic distribution in the other lipoproteins. As we recently reported, during normal gestation in women there is an increase in the cholesteryl ester transfer protein activity[67], which facilitates the exchange of triglycerides for cholesteryl ester between apoprotein B-containing lipoproteins (VLDL) and lipoproteins of higher density (low density lipoproteins, LDL, and high density lipoproteins, HDL). Throughout this mechanism, as also shown in Figure 5, during gestation there is an enrichment of triglycerides in both LDL and HDL[20], which are lipoprotein particles that normally do not transport triglycerides or do so in very small proportion. This, together with a decrease in the activity of hepatic lipase which is also seen during late gestation[66], seems to be responsible for the altered HDL subclass distribution seen in pregnant women during late gestation, with a specific increase in buoyant HDL_2 triglyceride-rich particles and decrease in small HDL_3[66].

BENEFITS OF MATERNAL HYPERTRIGLYCERIDEMIA FOR THE OFFSPRING

Triglycerides do not cross the placental barrier[10] but there are mechanisms by which both the fetus and the newborn could benefit from maternal hypertriglyceridemia.

The increase in plasma triglycerides during late gestation may represent an important floating energy source for rapid use under emergency conditions such as starvation, where they may be used as substrates for ketone body synthesis by the liver from which they are released into the circulation and easily cross the placenta to be used by the fetus, as commented above. Whereas the liver of the adult normally lacks LPL[50], as shown figure 6, in the liver of the 24 h fasted 20 day pregnant rat it appears an intense increase in LPL activity. A similar increase in liver LPL activity has been previously found after the intravenous administration of Intralipid to fasted nonpregnant rats[68], and has been interpreted as a result of the wash-out of extrahepatic LPL molecules which are carried to the liver by the triglyceride-rich lipoprotein remnants for their catabolism[68,69]. It is therefore proposed that a similar mechanism like the

in fetal development[70]. This action is further facilitated by the enhanced intestinal absorption of dietary triglycerides which is present during late pregnancy, as shown by studies in the 20 day pregnant rat[71].

A third and no less important benefit of maternal hypertriglyceridemia during gestation is its active contribution to milk synthesis in preparation of lactation[72]. As shown in Figure 7, after an oral load of labelled triglyceride there is a rapid and intense appearance of labelled lipids in the mammary gland of the late pregnant rat but not of virgin animal. Besides, by blocking the increase in mammary gland LPL activity after the treatment with progesterone in the late pregnant rat we have previously shown that the decline in plasma triglycerides normally occurring near parturition in the rat disappears[55]. These findings demonstrate that the rapid and intense induction in the mammary gland LPL activity that takes place around parturition facilitates the clearance of circulating triglycerides and their use in milk synthesis. Through this mechanism, essential fatty acids from the mother's diet circulating in the form of triglycerides become available to the suckling newborn, actively contributing to its development.

ACKNOWLEDGEMENTS

Present work has been supported in part with a grant from the Universidad San Pablo-CEU (grant 6/95). I thank Linda Hamalainen for her editorial help.

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