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Lipid Metabolism in Pregnancy

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Abstract. On the basis of bibliographic references and new own data, major adaptations of lipid metabolism occurring at late gestation are reviewed. Maternal hypertriglyceridemia at late gestation results from the juxtaposition of several factors: (1) enhanced adipose tissue lipolysis facilitating the availability to the liver of substrates for triglyceride synthesis and contributing to augmented flux of very low density lipoproteins (VLDL) into the circulation; (2) maternal hyperphagia and unmodified gut lipid absorption increasing chylomicron formation from dietary lipid; (3) reduced lipoprotein lipase (LPL) activity in extrahepatic tissues (especially adipose tissue) which does not allow a triglyceride removal proportional to their enhanced production. It is proposed that these changes are also responsible for the altered composition of VLDL in late pregnancy. In conditions of food deprivation the use of glycerol released from adipose tissue as preferential gluconeogenic substrate, and the enhanced maternal ketogenesis warrants the availability of fuels for the fetus. Just prior to parturition the increase in mammary gland LPL activity is responsible for the reduction in circulating triglycerides and prepares the mother for lactation.

Maternal body fat accumulated during the first half of gestation remains stable during late gestation [1–4] in spite of a continuous and intense draining of glucose, amino acids and other substrates to the fetus. These changes are associated with alterations in the endocrine system and a marked increase in maternal plasma lipids both in humans [5–8] and rats [9–14]. Free fatty acid (FFA) and triglyceride levels are very high in mother's plasma after the second trimester of gestation [5–15]. Since lipids have difficulties crossing the placenta [15], these changes occur mainly to fulfill maternal requirements although, in an indirect manner, they also facilitate passage of other substrates to the fetus.

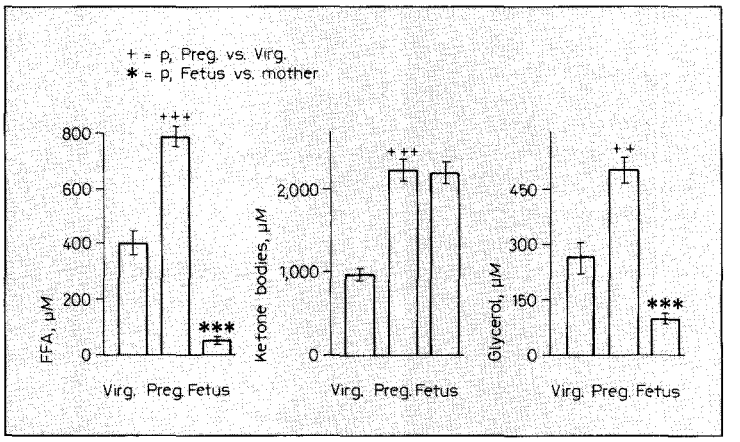

Fig. 1. Concentration of metabolites in plasma of 48 h starved virgin, 19-day pregnant rats and their fetuses. FFA were measured following the method of Falholt et al. [43], whereas ketone bodies and glycerol were estimated by enzymatic procedures [see 44, 45, respectively]. Means ± SEM of 6–8 rats/group.

The purpose of the present paper was to review the main changes responsible for maternal hyperlipemia and to clarify its consequences for the fetus, describing new experimental information concerning the maternal-fetal lipidic interactions at late gestation.

Maternal Adipose Tissue Lipolysis and Consequences to Fetal Nourishment

Adipose tissue lipolysis is enhanced in the mother at late gestation [16, 17] causing increased release into circulation of both FFA and glycerol which reach higher levels in maternal plasma [18, 19]. The liver is the main receptor of these two lipolytic products, as indicated by their specific rise in plasma after hepatectomy [19, 20]. In the liver, fatty acids are activated and used either for esterification in the synthesis of glycerides or for degradation to acetyl-CoA and ketone body synthesis through the β-oxidation pathway, whereas glycerol in its α-glycerol-phosphate form is used for glyceride glycerol synthesis or gluconeogenesis. In the fasting condition, both adipose tissue lipolysis and the metabolic use of its products are enhanced in the pregnant mother [11, 16] in a manner termed 'accelerated starvation' [4, 21]. Accordingly, as shown in figure 1, plasma levels of FFA, ketone bodies and glycerol are much higher in the starved late pregnant rat than in virgin controls. FFA concentration in fetal plasma remains low and similar to our reported findings in hepatectomized pregnant rats where FFA levels were highly enhanced in maternal plasma they remained low in the fetus [19], demonstrating the difficulties of these compounds in crossing the placental barrier. Ketone bodies freely cross the placenta and reach the same concentration in fetal as in maternal plasma (fig. 1). Since these compounds may be used as fetal fuels [22, 23] and even as substrates for brain lipid synthesis [24], they help to guarantee normal fetal development in conditions of maternal intense hypoglycemia as in the fasting state. Blood glycerol levels are lower in fetal than in maternal circulation probably as a consequence of its limited transfer through the placenta in comparison with other metabolites [25]. Increased

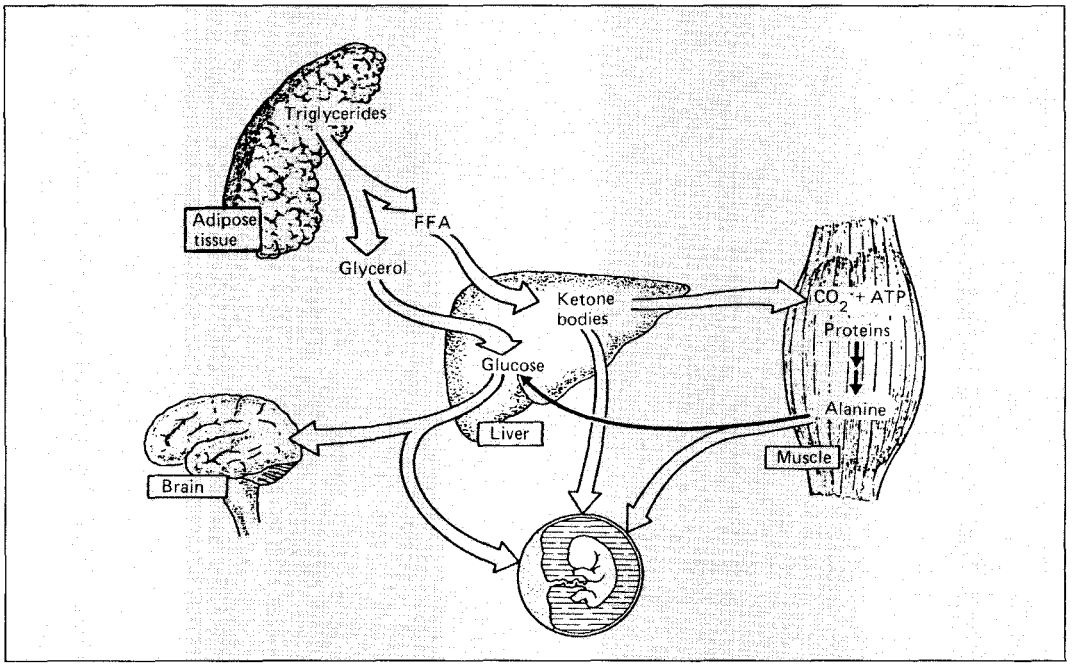

Fig. 2. Maternal response to starvation. Enhanced adipose tissue lipolysis increases the availability in the liver of glycerol to be used as a preferential substrate for gluconeogenesis and of FFA for ketone body synthesis. By this mechanism the mother conserves other gluconeogenic substrates such as alanine ensuring the adequate availability of fuels and metabolites to the fetus.

glycerol levels in maternal circulation function, however, as an effective and preferential substrate for glucose synthesis by the mother, as previously reported [18, 26]. Therefore, although indirectly, the fetus benefits from glycerol released to the mother's circulation by her enhanced adipose tissue lipolysis as it actively contributes to glucose synthesis in conditions of reduced availability of other substrates such as amino acids. These general changes occurring in the starved mother, and summarized in figure 2, show the critical role of maternal adipose tissue, accumulated during the first two thirds of gestation, on her metabolic adaptations during the last phase. Due to this energy store, the late pregnant mother continuously provides needed substrates to the fetus even if she is food deprived, while her own metabolic homeostasis is preserved by products of lipid metabolism in her own tissues.

Maternal Hypertriglyceridemia at Late Gestation as a Preparation for Lactation

While levels of all lipoprotein fractions in maternal plasma increase during the second half of gestation, increments in triglyceride-rich lipoproteins [chylomicrons and very low density lipoproteins (VLDL)] are among the most pronounced changes [6, 10, 13, 14, 27].

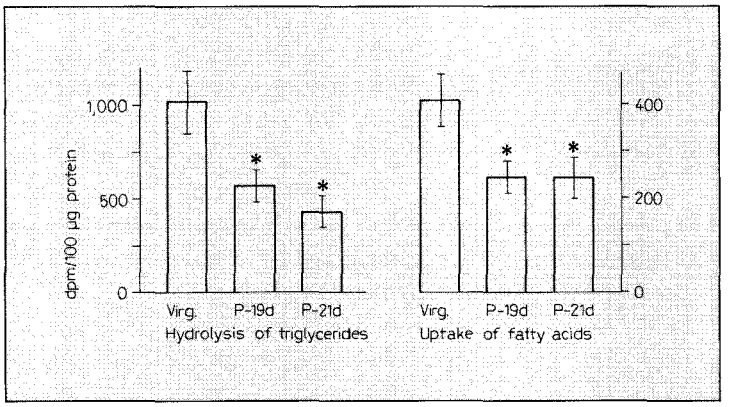

Fig. 3. Loss of saponifiable labelled neutral lipids from the media (hydrolysis of triglycerides) and appearance of labelled fatty acids in the adipocytes (uptake of fatty acids) in isolated adipocytes from 19- and 21-day pregnant rats (P-19d and P-21d) and virgin controls (Virg.) incubated for 60 min in the presence of rat plasma triglyceride-rich lipoproteins labelled with ^3H in their esterified fatty acids of neutral lipids (triglycerides). Other methodological details are as described previously [46]. Means ± SEM of 6 rats/group. Statistical comparisons of P-19d or P-21d vs. Virg.: * $p < 0.05$.

They are partially caused by an enhanced production of endogenous triglycerides [28–30] which, among other factors, is supported by the augmented transmission of FFA to the liver from adipose tissue lipolysis [16, 17]. A greater flow of dietary lipids into circulation may also contribute to maternal hypertriglyceridemia. Gastrointestinal transit is reduced at late gestation [31, 32] whereas lipidic gut absorption, which is not modified [33, 34], augments transmission of triglycerides from dietary fat [34] during the food intake increase typical in gestation [14, 35]. Decreased triglyceride removal cannot be ruled out as an additional factor contributing to maternal hypertriglyceridemia. Diminished adipose tissue lipoprotein lipase (LPL) activity [11, 14, 27, 36, 37] and post-heparin lipolytic activity at late gestation [14] are consistent with results summarized in figure 3, showing that isolated adipocytes from both 19- and 21-day pregnant rats have reduced capacity to hydrolyze triglyceride fatty acids from triglyceride-rich lipoproteins and consequently a reduced uptake of these substances. Concomitant increase in triglyceride entry and delayed removal from circulation may not only augment maternal hypertriglyceridemia but modify the proportional distribution of circulating VLDL subfractions. As shown in figure 4, the heparin-Sepharose chromatographic profiles of plasma VLDLs purified from normal virgin rats and eluted with media containing NaCl at different concentrations show three main peaks: B, C and D, respectively eluting with 0.12, 0.20 and 0.50 *M* NaCl, the last one being the highest. When the same separation is performed with plasma from 20-day pregnant rats, the pattern changes and peak B is clearly the highest. Different retentions of these subfractions in the heparin-Sepharose column correspond to differences in their apoprotein content, enrichment in apopro-

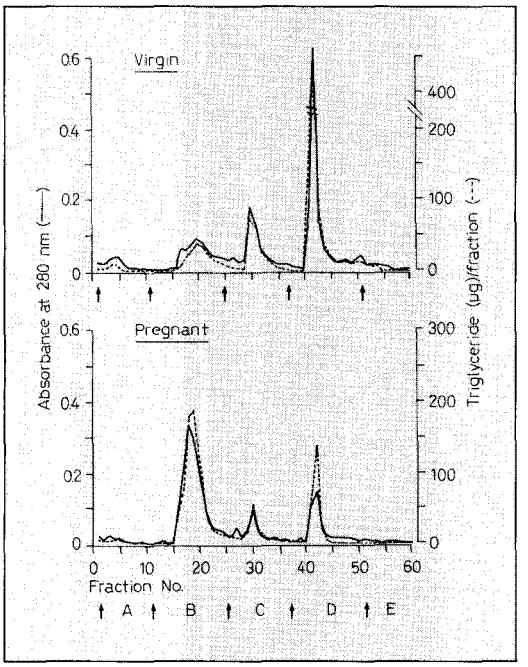

Fig. 4. Elution profile from heparin-Sepharose column in 5 m*M* Tris buffer, pH 7.4, supplemented with 0.05 (A), 0.12 (B), 0.20 (C), 0.50 (D) or 1.00 *M* NaCl (E) of VLDL (d < 1.006) purified by ultracentrifugation from plasma of 20-day pregnant and virgin rats. The amount of VLDL triglycerides placed into each column was the same for both groups (1.8 mg VLDL triglyceride/column). Volume per fraction = 1 ml. The figure corresponds to a representative result from 4 different experiments performed in each group of animals.

tein E being the main factor causing greater binding to the column [38]. The physiological significance of these differences is not yet known but it indicates that the composition and subfraction distribution of maternal VLDL undergo important modifications which may contribute to or be a consequence of the modified VLDL turnover at late gestation, producing stable hypertriglyceridemia.

Maternal hypertriglyceridemia has an important role as a source of triglycerides for milk formation just before parturition. At this time a sharp reduction in maternal circulating VLDL levels occurs when adipose tissue LPL activity is still low [27] and the rate of entry of triglycerides into the circulation is still high [10]. This effect is associated with increased mammary gland LPL activity as it was completely abolished when the increase was blocked by progesterone treatment [27], and it has been directly demonstrated that it increases the uptake of circulating triglycerides by this gland in the late pregnant rat [34] even before its lipogenetic activity is enhanced [39]. Similar changes may occur in pregnant women prior to lactation [40].

Conclusion

The major changes occurring in the mother during the second half of gestation which are responsible of her triglyceridemia are summarized in figure 5. Enhanced adipose tissue lipolysis facilitates the availability to the liver of substrates for triglyceride formation which, together with endogenous changes, promote enhanced flux of triglycerides into the circulation in the form of VLDL. This pool of triglycerides is enriched by chylomicron triglycerides from dietary lipids, the production of which is also augmented as a result of the maternal hyperphagia and unmodified gut lipid absorption. Hypertriglyceridemia remains stable until late gestation because reduced LPL activity in the extrahepatic tissues (especially adipose tissue) does not permit removal of triglycerides proportional to its enhanced production. These changes, together with mater-

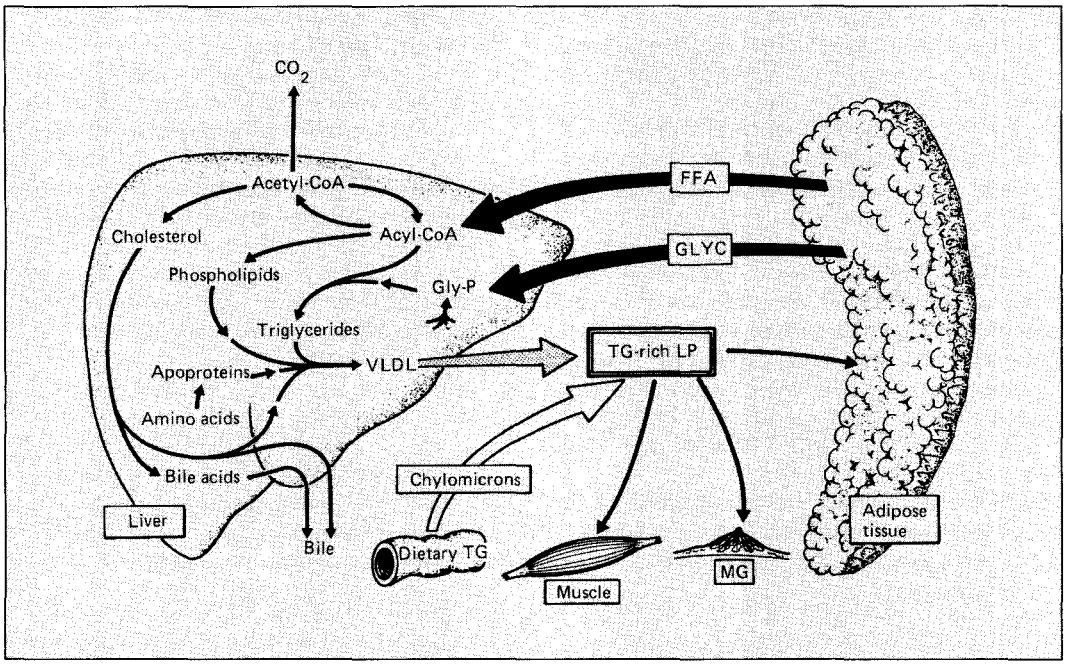

Fig. 5. Summary of major changes in maternal lipid metabolism at late gestation.

nal energy stores (mainly in the form of fat deposits), contribute to fulfill maternal and fetal metabolic needs. In conditions of maternal food deprivation, the use of glycerol released from adipose tissue as a preferential gluconeogenetic substrate together with the enhanced maternal ketogenesis demonstrate the important contribution of maternal fat to ensure the availability of fuels for the fetus. These conditions are modified shortly prior to parturition because an increase in mammary gland LPL activity (probably mediated by the augmented prolactin release which occurs before parturition [27, 41, 42]) facilitates the uptake of circulating triglycerides to the gland, causing a reduction in circulating triglycerides and preparing the mother for lactation.

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