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MATERNAL LIPID METABOLISM AND ITS IMPLICATIONS FOR FETAL GROWTH

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ABSTRACT

Glucose is the most abundant nutrient crossing the placenta and the use of both glucose and amino acids by the fetus is essential to sustain intrauterine development. Nevertheless, changes in lipid metabolism during gestation also play a key role in the development of fetal fat mass and subsequent growth. During early pregnancy there is an increased accumulation of fat depots in the mother, which is switched to an active adipose tissue breakdown in late pregnancy; these changes are responsible for the maternal hyperlipidemia that is normally present during the last third of pregnancy. The changes are controlled by different hormones, but the biphasic changes in insulin sensitivity taking place during pregnancy seem to play a major role. Maternal hyperlipidemia mainly results from an increase in TAG-rich lipoproteins, which transport LCPUFA in particular mainly in their esterified form. Lipoproteins in maternal plasma don't cross the placenta directly, but the presence of lipoprotein receptors, fatty acid binding proteins and different lipases allow the transfer of LCPUFA to the fetus.

KEYWORDS: Maternal lipid metabolism, fetal growth.

INTRODUCTION

There is increasing recognition that maternal glucose concentrations lower than those previously used for the diagnosis of gestational diabetes mellitus (GDM) and targeted for treatment can result in excess fetal growth. Yet, mothers with GDM who appear to have optimal glycemic control and mothers with obesity and normal glucose tolerance still have a significantly increased risk for delivering infants who are large for gestational age, or even more importantly, who have increased adiposity at birth. What is less appreciated is that in addition to glucose, maternal lipids are also substrates for fetal fat accretion and that placental

lipases can hydrolyze maternal triglycerides (TGs) to free fatty acids for fetalplacental availability. Maternal TG levels are 40% to 50% higher on average in mothers with obesity and GDM compared to those in normal-weight mothers early in pregnancy and are sustained at higher levels throughout gestation.[1]

Increasing evidence supports that maternal TG, both fasting and postprandial, are also predictors of newborn adiposity (newborn %fat), a risk factor for childhood obesity, and that early exposure is at least as strong of a risk factor as later exposure in mothers with obesity. In the setting of maternal nutrient excess and maternal insulin resistance, which lead to fetal hyperinsulinemia, excess free fatty acid exposure in the fetus may result in lipid storage and fetal fat development in subcutaneous and possibly other depots. In this commentary, we provide further evidence to make a case for targeting maternal fasting and postprandial TG in mothers with obesity who have elevated TG in early pregnancy to determine whether a TG-lowering.[2]

Increasing data suggest that intrauterine factors that contribute to excess fetal growth, a risk factor for childhood obesity, are not limited to maternal glucose availability. Mothers with gestational diabetes mellitus (GDM) who appear to have optimal glycemic control1 and mothers with obesity and normal glucose tolerance still have a significantly increased risk for delivering infants who are large for gestational age (LGA).[3] Maternal lipids may play an important role in excess fetal fat accretion, but studies to date have been inconclusive. Maternal triglycerides (TGs) and free fatty acids (FFAs) have been identified as important lipid contributors to increased birth weight (BW) and LGA, but whether their elevation in the fasting versus the postprandial state is a stronger predictor of excess growth has been inadequately studied.[4]

The majority of studies in which the role of maternal lipids on fetal growth have been examined have not controlled for diet, which markedly affects lipids, particularly TG. Furthermore, they have measured BW. It has become clear that BW is not an accurate surrogate for newborn body composition and that the percentage of fat in a newborn (newborn %fat) is a better predictor of later childhood obesity than is BW.[5]

In this commentary, we review some of the data that offer a strong case for excess maternal TG and FFA to be important and relatively unrecognized substrates for fetal fat accretion and

fetal overgrowth making fat from fat. Potential therapeutic strategies that can target and reduce fasting and postprandial TG, similar to those applied in GDM, are proposed.

BACKGROUND

In pregnancy, lipids were classically thought to primarily provide energy substrate to support maternal energy needs given that glucose is shunted to support fetal growth. However, as hepatic de novo lipogenesis (glucose! lipid) is considered marginal in the fetal liver,10 and the fetus has a limited mitochondrial capacity to oxidize FA,[6] lipids provide an important fuel for fetal fat accretion, especially in the late 2nd and 3rd trimesters, when adipogenesis accelerates. Coordinated by placental hormones, normal pregnancy metabolism is characterized by a marked increase in insulin resistance (IR), increased postprandial glucose, a 2- to 3-fold increased insulin production,[7] and increased plasma FFAs, TGs,6 total cholesterol, and phospholipids, similar to metabolic syndrome as defined outside of pregnancy.[8]

Increases in maternal TGs (2- to 3-fold), phospholipids, and FFAs occur with advancing gestation and are even higher in mothers with obesity and GDM. The switch to increased adipose tissue IR in later pregnancy results in lipolysis and FFA release. Along with dietary chylomicron (CM)-TG, this serves to further increase the maternal and fetal- placental availability of TGs and FFAs. placenta secretes large quantities of estrogen that stimulate hepatic very low-density lipoprotein (VLDL)- TG production, further promoting the doubling of maternal TGs.[9]

In addition to maternal IR in mothers with obesity that promotes modestly higher fasting and postprandial glucose, maternal IR also affects adipose tissue by increasing maternal lipolysis rather than storing fat, resulting in excess TGs and FFAs in the maternal circulation available to the fetalplacental unit.24 We and others have shown that in pregnancies affected by obesity, these processes are often already present in many women, given that obese women have »10% higher 24-hour glucose patterns, »30% to 40% higher TGs,and 40% to 50% higher IR compared to normal weight (NW) early in pregnancy, providing an early higher overall nutrient gradient to the fetalplacental unit6.[10]

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.[11] The increase in maternal fat depots seems to be mainly a result of enhanced lipogenesis, which has been demonstrated both in vivo and in periuterine adipose tissue in situ; 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[12], 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; (b) lipolytic activity becomes highly enhanced[13] because of increased activity by the key enzyme in the lipolytic cascade, hormone-sensitive lipase (HSL); and (c) tissue uptake of circulating triglycerides decreases because of reduced lipoprotein lipase (LPL) activity.[14]

The adipose tissue HSL-to-LPL messenger RNA and activity ratios appear enhanced during late gestation, 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.[15] Placental transfer of these two lipolytic products is low, and maternal liver is their main receptor[16], 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 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, 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 (Fig. 1).

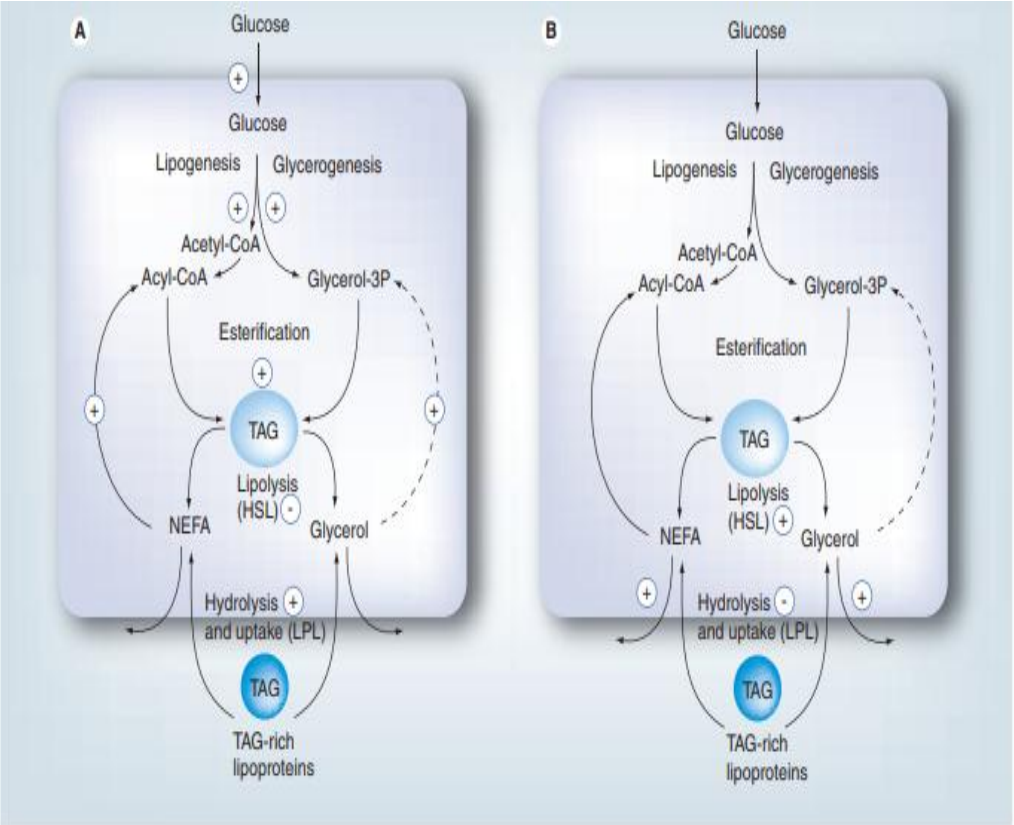

Figure 1. Adipose tissue metabolism during pregnancy. Schematic representation of the main changes taking place in maternal adipose tissue metabolism during early **(A)** and late pregnancy **(B)**. Most of the proposed changes are driven by the changes in insulin sensitivity taking place during these two stages of pregnancy. + and – signs, respectively, indicate enhanced and decreased pathways. Additional details in the text.

Ketone body synthesis becomes highly enhanced during late pregnancy under fasting conditions[17], 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.[18]

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 the maternal circulation, the fetus greatly benefits from the end metabolic products of maternal adipose tissue lipolytic activity. Ketone bodies freely cross the placenta and may be used as fetal fuels or even as substrates in brain lipid synthesis.[19]

The efficient transfer of glucose to the fetus 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. 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, and the lipolytic products—especially FFA and ketone bodies—can be used as alternative fuels to spare glucose.[20]

MATERNAL FAT ACCUMULATION

The accumulation of fat in maternal depots occurs during the first two-thirds of gestation. Maternal hyperphagia increases the availability of substrates, which together with higher insulin levels and even enhanced insulin sensitivity during early pregnancy, results in enhanced lipogenesis.[21]

A second factor that appears to contribute to the accumulation of fat depots during early pregnancy is the increasd activity of adipose tissue lipoprotein lipase (LPL). This enzyme, anchored in its active form in the capillary endothelium of extrahepatic tissues, hydrolyzes TAG circulating in plasma in the form of TAG-rich lipoproteins (i.e., chylomicrons and VLDL), and the hydrolytic products, fatty acids and glycerol, are mostly taken up by the subjacent tissue.[22]

In this way, LPL activity is a prerequisite for the uptake of fatty acids from circulating TAG by adipose tissue, its increase during early pregnancy would also contribute to the accumulation of lipids in maternal depots. The increase in fat depot accumulation stops or even declines during the last third of gestation[23], as a consequence of both enhanced adipose tissue lipolytic activity (see later) and decreased adipose tissue LPL activity. It has been found in late pregnant women that postheparin LPL activity decreases during the third trimester of gestation, and studies in late pregnant rats found that such a change corresponded to a decrease in the activity of the enzyme in adipose tissue.[24] Thus, the anabolic condition present in adipose tissue during early pregnancy switches to a net breakdown of maternal lipids, which is coincident with the highest rate of fetal growth.

The Effects of Placental LPL Activity and Angiopoietinlike Protein 4 (ANGPTL4) on Neonatal fat Mass

During the second half of pregnancy the placental transfer of LCPUFA is increased and the fetus deposits them rapidly as fat.[25] As already mentioned, most of the LCPUFA are carried in maternal plasma as an esterified form by different lipoproteins. After being recognized by specific receptors in the placenta, the lipoprotein lipids have to be hydrolyzed by one of the

different lipases before the transfer of fatty acids to the fetus can take place. LPL is one such lipase; it is expressed in both adipose tissue and placental tissue, where it catalyzes the hydrolysis of plasma VLDL-TAG to supply NEFA and glycerol for the synthesis of TAG in adipocytes.[26]

Alterations in placental LPL activity have been associated with changes in the transport of fatty acids to the fetus affecting its growth. Thus, an increase in placental LPL has been reported in type 1 diabetes with large for gestational age neonates; conversely, there was a reduction of placental LPL activity in pregnancies complicated by intrauterine growth restriction[27], which is normally characterized by reduced fetal fat depots. Since no correlation between placental LPL gene expression and neonatal birth weight or gestational age have been found, it was proposed that altered LPL in those conditions is due to modulation of its activity at the post-transcriptional stage.[28]

The activity of some lipases is regulated by the action of members of the angiopoietin-like (ANGPTL) protein family. One of these proteins, ANGPTL4, is secreted into the blood from adipose tissue, liver and placenta and has been shown to inhibit LPL activity irreversibly by converting active LPL dimers into inactive monomers.[29]

As hypertriacylglycerolemia and tissue-specific changes in LPL activity are routinely found during late pregnancy[30], the potential relationship of maternal and fetal plasma ANGPTL4 concentrations to newborn growth, fat mass and serum TAG was studied in GDM pregnant women and their offspring. It was found that GDM pregnant women, who delivered newborns with high fat mass, had high concentrations of both TAG and NEFA and low concentrations of ANGPTL4 in the maternal serum, despite glucose and insulin concentrations were independent of changes in neonatal fat mass. When the pregnant women with GDM having neonates with the highest fat mass were studied, their neonates were found to have lower concentrations of TAG and no differences in NEFA or ANGPTL4, but did have high insulin concentrations.[31]

It was therefore concluded that an enhanced LPL activity in the placenta at late pregnancy in GDM is facilitated by the reduction of ANGPTL4 in the maternal circulation. The increases in maternal TAG concentrations in GDM women, whose newborns had the highest fat mass, corresponded to the lowest TAG concentrations in cord serum. This steeper materno-fetal TAG gradient in the presence of higher LPL activity could have been facilitating a greater

transfer of fatty acids across the placenta, which in turn would contribute to the higher fetal fat accumulation. However, since changes in newborns with high fat mass from GDM mothers appeared in the absence of any difference in ANGPTL4 concentration it was proposed that the potential inhibitory effect of this protein on their adipose tissue LPL activity was overcome by their hyperinsulinemia.[32]

CONCLUSIONS

Fetal growth depends on maternal metabolic factors, glucose being the substrate, which crosses the placenta in greatest quantities and is used as the principal oxidative substrate by the fetus. Although a relationship between maternal plasma glucose levels and fetal growth has been found in both healthy and diabetic women[33], there are also reports where no such correlation has been found indicating that other factors besides the availability of glucose actively contribute to fetal growth. Alternatively, although lipids cross the placental barrier with difficulty, changes in lipid metabolism taking place on the maternal side could also contribute to fetal development and it has been reported that maternal triacylglycerols (TAG) and nonesterified fatty acids (NEFA) correlate with cord blood lipids and fetal growth.

Lipid metabolism greatly changes during physiologic pregnancy, but the way in which these changes affect lipid deposition in the adipose tissue of the fetus and its subsequent growth is not completely understood. The availability of substrates in the fetus depends on their concentration in the maternal circulation and to the extent they are transported across the placenta. Thus, maternal hyperlipidemia during pregnancy facilitates the availability of lipids to the fetus and could also contribute to its accumulation in fat depots, as suggested by the correlations found between maternal NEFA and TAG close to delivery versus cord blood lipids and neonatal weight and fat mass, in well-controlled gestational diabetic (GDM) women.[34]

Oxidative stress is present in normal pregnancies and could be the result of maternal hyperlipidemia. However, increments of oxidative stress indices over control values have been associated with altered pregnancy outcome, as has been shown in diabetes, preeclampsia and intrauterine growth restriction (IUGR).[35]

Although there is no consensus on the pathophysiological events underlying oxidative stress in these conditions, it has been proposed that supplements with antioxidants during pregnancy may be beneficial for both the mother and her fetus. On the basis of the

importance of maternal lipids on fetal development, this article reviews major changes in lipid metabolism that occur during normal pregnancy and their implications in fetal development.

Adipose tissue metabolism during pregnancy schematically summarizes the main changes taking place in maternal adipose tissue during early pregnancy, which are mainly the result of the enhanced insulin sensitivity that takes place at this stage. From studies in rats, it is known that the antilipolytic action of insulin in adipose tissue is enhanced during early pregnancy, which is in line with the reported increase in insulin sensitivity that has been found in the first third of gestation in women.[36]

Another alteration that contributes to the anabolic changes present in adipose tissue during early pregnancy is the unique capacity of the tissue to reutilize intracellularly the glycerol released throughout lipolysis. Under normal conditions, the negligible glycerol kinase activity in adipose tissue impedes the utilization of glycerol for glycerol-3-phosphate synthesis and its use for the synthesis of TAG.[37]

However, an increase in glycerol kinase activity and its subsequent capacity to metabolize glycerol has been found in rodents under conditions of hyperinsulinemia and enhanced fat accumulation, such as obesity. More recently, it has been reported that the in vitro capacity of adipose tissue to take up not only glucose but also glycerol and to convert them into glyceride glycerol is significantly enhanced in 7-day pregnant rats compared with nonpregnant or late pregnant rats.[38] The lower lipolytic activity together with the augmented capacity of the tissue for the synthesis of glycerol3-phosphate for TAG synthesis from both glucose and intracellular released glycerol results in a net intracellular accumulation of TAG. These changes combined with the enhanced lipogenesis and LPL activity controlling the hydrolysis of circulating TAG and uptake of its products (NEFA and glycerol), explains the enhanced accumulation of fat depots that occurs during the first part of pregnancy. Since all these pathways are stimulated by insulin, it is proposed that the enhanced insulin responsiveness in the presence of an augmented response of the pancreatic b cells to the insulinotropic stimulus of glucose that has been found both in early pregnant women would be the principal driving force for the net fat depot accumulation at this stage of pregnancy.

The anabolic condition of adipose tissue during early pregnancy switches to a net catabolic condition during the last third of gestation, as shown by a higher adipose tissue lipolytic

activity and lower LPL activity.[39] These changes taking place in maternal adipose tissue metabolism during late pregnancy have been schematically summarized in Figure 1B. The presence of high plasma levels of placental hormones known to have lipolytic effects (i.e., human placental lactogen), an augmented production of cathecholamines secondary to maternal hypoglycemia and the insulin-resistant condition present at this stage[40], appears to be responsible for the net breakdown of maternal fat depots, consistently causing increments in plasma NEFA and glycerol levels during the third trimester of pregnancy.

Accumulation of Fat in Maternal Tissues

During the first two-thirds of gestation, maternal hyperphagia, higher concentrations of insulin in the blood and unchanged or increased insulin sensitivity result in increased adipose tissue fatty acid synthesis, as reported in rats. During this early stage of pregnancy there is also an increase in adipose tissue lipoprotein lipase (LPL) activity, which catalyzes the hydrolysis of circulating TAG that is carried in TAG-rich lipoproteins (i.e. chylomicrons and very low-density lipoproteins (VLDL)). The hydrolytic products, NEFA and glycerol, are mostly taken up by the subjacent tissue. Overall these changes facilitate the accumulation of lipids in maternal depots, as has been seen consistently in both humans and rats.[41]

During the last third of pregnancy the accumulation of fat depots in maternal tissues stops or even declines as result of both an increased lipolysis and mobilization of TAG stored in adipose tissue (see below) and a decreased activity of adipose tissue LPL.[42]

Thus, the anabolic condition is seen in adipose tissue during early pregnancy switches during late pregnancy to a net breakdown of maternal fat depots. These changes coincide with a change in insulin sensitivity, which decreases consistently during late pregnancy in both humans[43] and rats. Studies in the rat have demonstrated that these biphasic changes in insulin sensitivity during pregnancy are directly involved in (or responsible for) the changes in maternal adipose tissue metabolism.[44]

Adipose Tissue Metabolism

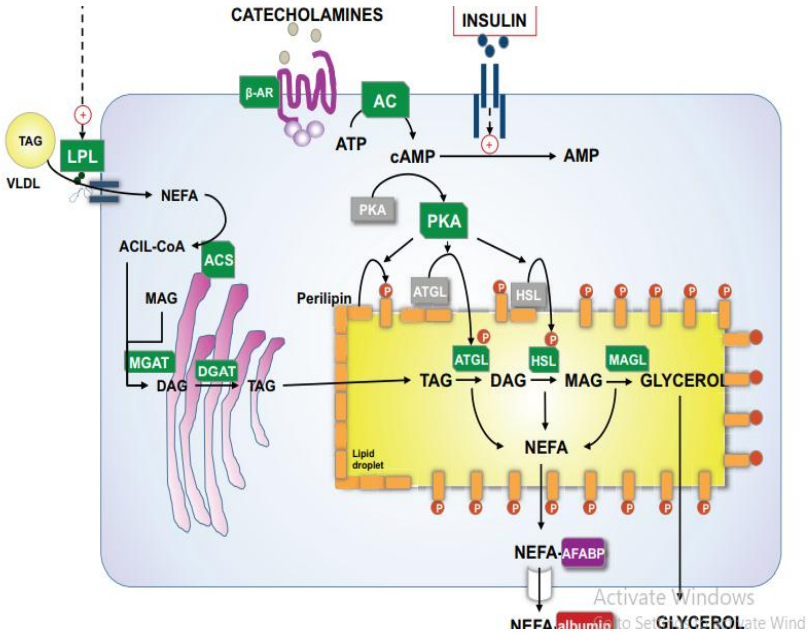

Fig. (2) summarizes the main pathways of adipose tissue metabolism. It shows the effects of the two hormones that exert the most active control on adipose metabolism. Insulin controls the uptake of circulating TAG-rich lipoproteins by increasing LPL activity and decreasing the adipocytes' lipolytic activity, achieved by increasing the conversion of cAMP into AMP. Catecholamines increase the activity of the lipolytic cascade by interacting with the β-adrenergic receptors, thereby increasing the production of cAMP. During early pregnancy the increase in insulin sensitivity that has been found in both women and rats increases the anti-lipolytic action of insulin.[45]

It also increases the capacity of adipose tissue to take up glucose from the circulation and to reutilize the glycerol released by lipolysis. Taken together, these effects, and the increased fatty acid synthesis and LPL activity already mentioned, result in the increased synthesis and accumulation of TAG that takes place in the early stages of pregnancy. During the last third of gestation, the increases in placental hormones with lipolytic effects in maternal plasma, an increase in the production of cathecholamines secondary to maternal hypoglycemia[46] and the development of insulin resistance are together responsible for the net breakdown of maternal fat depots and the consequent increments in plasma NEFA and glycerol concentrations. The main destination of these lipolytic products is the liver, where they are converted into their active forms (i.e. acylCoA and glycerol-3-phosphate) and a proportion are reesterified for the synthesis of TAG, which is released back into the circulation as a component of VLDL particles. A certain proportion of the acyl-CoA in the liver may be

routed to the beta-oxidation pathway resulting in energy production and the synthesis of ketone bodies; glycerol is also used for gluconeogenesis. These two pathways are greatly accelerated under fasting conditions in late pregnancy[47], and represent a benefit to the fetus. Ketone bodies, on the one hand, are used by maternal tissues, and thereby conserve glucose for essential functions (i.e., its use by tissues that depend on glucose, like brain and erythrocytes); on the other hand, they easily cross the placenta and can be used by the fetus as oxidative fuels as well as substrates for brain lipid synthesis. The use of glycerol for glucose synthesis also benefits the fetus because glucose is the most abundant nutrient to cross the placenta and is the main oxidative substrate used by the fetus.

Insulin is well-known to inhibit adipose tissue lipolysis and hepatic gluconeogenesis and ketogenesis, but increases adipose tissue LPL activity. The insulin-resistant condition of late pregnancy therefore appears to cause all the characteristic catabolic changes observed at this stage. Maternal Hyperlipidemia During late pregnancy there is normally a rise in plasma TAG, with smaller rises in phospholipids and cholestero. The greatest component of the increase in plasma TAG corresponds to VLDL, although they also accumulate in both low density and high-density lipoproteins (LDL and HDL). The abundance of VLDL-TAG is a consequence of their increased production by the liver and of their decreased clearance from circulation due to low LPL activity.[48]

This increased availability of VLDL-TAG and the increased activity of cholesteryl ester transfer protein (CETP) that appears in mid-pregnancy facilitate the exchange of VLDL-TAG for esterified cholesterol from LDL and HDL. This, together with a decrease in hepatic lipase that occurs during late pregnancy, explains the accumulation of TAG in LDL and HDL, which normally, under nonpregnant conditions, contain much less TAG. The hormonal factors responsible for the metabolic changes of pregnancy, resulting in the development of maternal hypertriacylglycerolemia, are the insulin-resistance and the increase in plasma estrogen concentrations that occur during late pregnancy.[49]

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