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Lipid Metabolism During Pregnancy and its Implications for Fetal Growth

Emilio Herrera* and Henar Ortega-Senovilla

Faculties of Pharmacy and Medicine, Universidad San Pablo CEU, Madrid

Abstract: More glucose crosses the placenta than any other substrate, but correlations between its concentration in maternal plasma and fetal growth are not found consistently. The accumulation of maternal fat depots and hyperlipidemia are the two principal changes in lipid metabolism during pregnancy. Although lipids cross the placenta with difficulty, maternal plasma triacylglycerols (TAG) and non-esterified fatty acids (NEFA) correlate with fetal lipids, fetal growth and fat mass under certain conditions. In intrauterine growth restriction, impaired placental transfer of lipophilic compounds (long-chain polyunsaturated fatty acids and lipophilic vitamins) seems to underpin metabolic dysfunction and decreased birth weight. In gestational diabetes mellitus (GDM), maternal TAG and NEFA levels correlate with neonatal anthropometric measures. In GDM, adipocyte fatty acid-binding protein in fetuses correlated with neonatal fat mass; changes in maternal or cord blood leptin, retinol binding protein 4 and adiponectin concentrations have been related to neonatal fat mass or birth weight, although their importance remains to be investigated. The angiopoietin-like protein 4 (ANGPTL-4) is secreted from adipose tissue, liver and placenta, and irreversibly inhibits lipoprotein lipase (LPL) activity. Maternal plasma ANGPTL-4 is decreased in GDM, and it has been proposed to be responsible for an increase in placental LPL activity, which would facilitate a greater fatty acid placental transfer, contributing to the higher fetal fat accumulation. Thus, while evidence suggesting major involvement of maternal lipid metabolism in fetal adiposity and growth exists, the precise mechanisms remain to be elucidated.

Keywords: Adipocytokines, adipose tissue, gestational diabetes mellitus, hyperlipidemia, intrauterine growth restriction, non-esterified fatty acids, placenta, pregnancy.

INTRODUCTION

During gestation, glucose is the substrate that crosses the placenta in the greatest quantities and a relationship between maternal plasma glucose concentrations and fetal growth has been found in both healthy [1] and diabetic women [2-5]. However, this correlation has not always been found [1, 6-8] indicating that other factors may also contribute to fetal growth. Lipids cross the placenta with difficulty [9] but plasma concentrations of maternal triacylglycerols (TAG) and non-esterified fatty acids (NEFA) have been shown to correlate with fetal lipid concentrations and fetal growth [10-12]. As recently reviewed [13], in women with gestational diabetes (GDM) a wide range of dyslipidemic conditions are present, and a positive correlation between maternal TAG concentrations and neonatal body weight or fat mass has been found even in normoglycemic conditions. Changes in the amounts and relative proportions of endocrine, paracrine and autocrine proteins secreted by white adipose tissue (collectively termed adipocytokines) have been observed in women with GDM and associated with adverse outcomes under normoglycemic conditions [13].

Throughout pregnancy there are major changes in maternal lipid metabolism [14, 15] and a maternal hyperlipidemia is normally developed during the last third of gestation, but the way these changes affect fetal fat mass and subsequent growth of the fetus is not completely understood. Since the availability of substrates in the fetus depends on their concentration in maternal circulation, such hyperlipidemia facilitates the availability of lipids to the fetus. In fact, the correlation between maternal NEFA and TAG concentrations close to delivery with fetal plasma lipids and neonatal weight and fat mass found in well-controlled GDM women [12] demonstrate that maternal hyperlipidemia could contribute to the availability of lipids to the fetus and its accumulation in fat depots.

By way of its action on insulin-sensitive tissues (skeletal muscle, liver, heart, adipose tissue), fetal insulin could regulate fetal lipid metabolism and subsequent fetal growth. In fact, fetal insulin is low in fetuses with intrauterine growth restriction (IUGR) and in those that are small for gestational age (SGA) [16] whereas it is high in diabetic pregnancies [17], especially when the fetus is large for gestational age (LGA) [12]. However, no correlation between fetal insulin and fetal fat mass has been detected [18].

In an attempt to advance the understanding of the importance of maternal lipids to fetal development, this article reviews major changes in lipid metabolism and adipocytokines, and their implications for fetal development, that take place both during normal pregnancies and in two conditions where altered fetal growth occurs: intrauterine growth restriction and gestational diabetes with satisfactory glycemic control. The objective is to advance the understanding of the importance of maternal lipids for fetal development. Although most of the cited articles refer to studies carried out

*Address correspondence to this author at the Universidad San Pablo CEU, Ctra. Boadilla del Monte km 5.3, 28668 Madrid, Spain; Tel: +34-913-724-730; Fax: +34-913-510-496; E-mail: eherrera@ceu.es

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with humans, some information is derived from studies in rodents. Many, but not all, of the metabolic changes taking place during the first, second and third thirds of gestation in rodents appear to be similar to those occurring during the corresponding trimesters of pregnancy in humans [19-21], but extrapolations should be done with caution.

LIPID METABOLISM IN NORMAL PREGNANCY

The accumulation of fat in maternal depots that occurs during early pregnancy [22, 23] and the later development of hyperlipidemia [14] are the two principal changes in lipid metabolism that occur during pregnancy.

Accumulation of Fat in Maternal Tissues

During the first two-thirds of gestation, maternal hyperphagia [24], higher concentrations of insulin in the blood and unchanged or increased insulin sensitivity [25-27] result in increased adipose tissue fatty acid synthesis, as reported in rats [28]. During this early stage of pregnancy there is also an increase in adipose tissue lipoprotein lipase (LPL) activity [29], which catalyzes the hydrolysis of circulating TAG that are 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 [30]. Overall these changes facilitate the accumulation of lipids in maternal depots, as has been seen consistently in both humans [23] and rats [22].

During the last third of pregnancy the accumulation of fat depots in maternal tissues stops or even declines [22, 31] 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 [14, 31, 32]. Thus, the anabolic condition 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 [27], which decreases consistently during late pregnancy in both humans [33, 34] and rats [35]. 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 [27, 36].

Adipose Tissue Metabolism

Fig. (**1**) 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 [25, 26] and rats [27, 35] increases the anti-lipolytic action of insulin [27]. It also increases the capacity of adipose tissue to take up glucose from the circulation and to reutilize the glycerol released by lipolysis [37]. 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 [38] in maternal plasma, an increase in the production of cathecholamines secondary to maternal hypoglycemia [39] and the development of insulin resistance [34, 40] 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 [41], where they are converted into their active forms (i.e. acyl-CoA and glycerol-3-phosphate) and a proportion are re-esterified for the synthesis of TAG, which are released back into the circulation as a component of VLDL particles.

A certain proportion of the acyl-CoA in 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 [42, 43], 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 [44]. The use of glycerol for glucose synthesis also benefits the fetus because glucose is the most abundant nutrient to cross the placenta [45, 46] and is the main oxidative substrate used by the fetus [47].

Insulin is well-known to inhibit adipose tissue lipolysis (Fig. (**1**)) 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 [33, 35, 48, 49].

Maternal Hyperlipidemia

During late pregnancy there is normally a rise in plasma TAG, with smaller rises in phospholipids and cholesterol [50]. 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) [14]. The abundance of VLDL-TAG is a consequence of their increased production by liver [51] and of their decreased clearance from circulation due to low LPL activity [14, 52]. This increased availability of VLDL-TAG and the increased activity of cholesteryl ester transfer protein (CETP) that appears in mid-pregnancy [14, 53] 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 [14], explains the accumulation of TAG in LDL and HDL, which normally, under non-pregnant 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 [13].

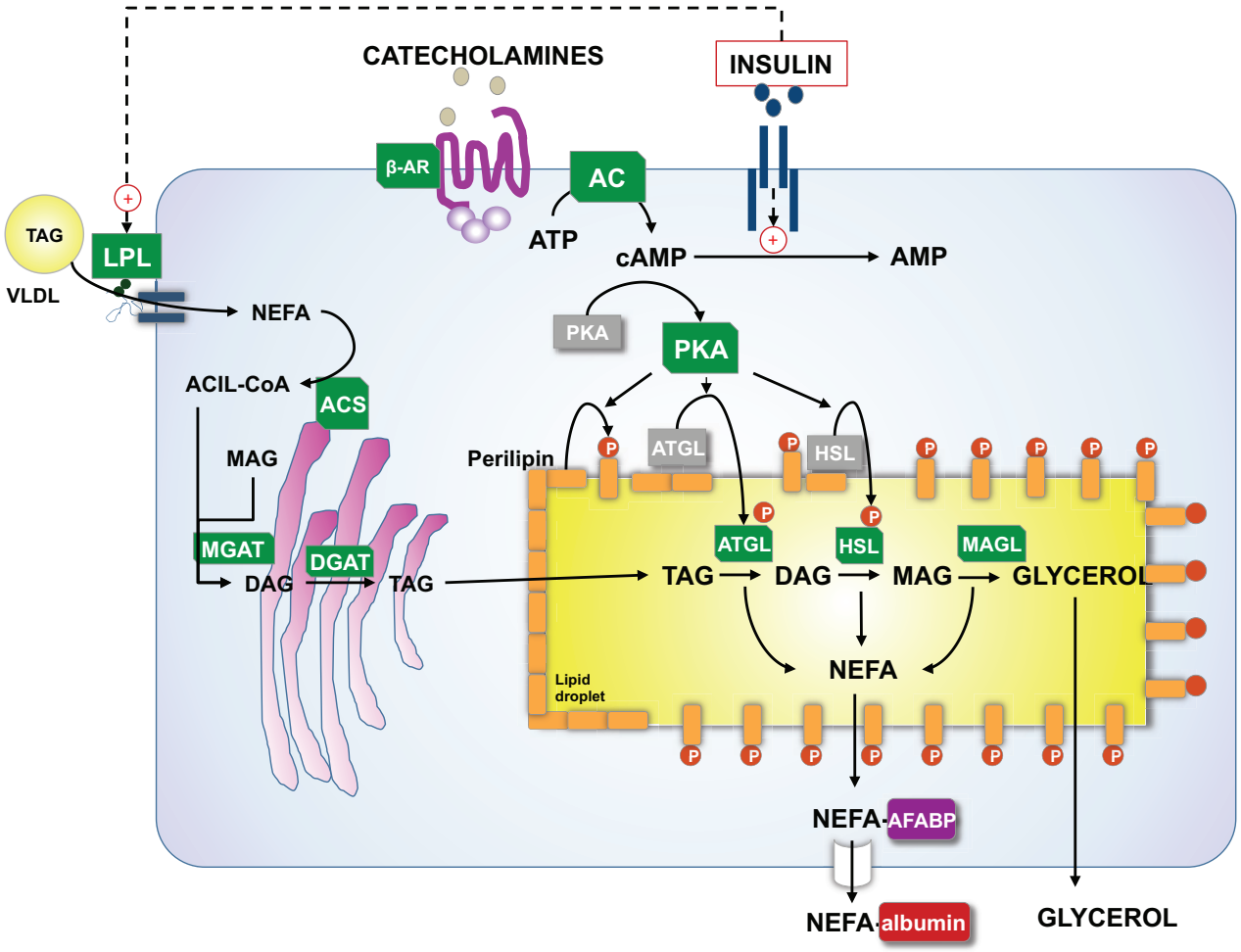

Fig. (1). Schematic overview of adipose tissue lipolysis and the uptake of circulating triacylglycerol-rich lipoproteins (mainly VLDL) and their control by catecholamines and insulin. The binding of catecholamine to the β-adrenergic receptors (β-AR), couples to the adenylate cyclase (AC) via the stimulatory G-protein, which activates adenylate cyclase and increases the production of cyclic AMP (cAMP). This leads to the activation of protein kinase A (PKA), which phosphorylates and activates several key proteins including perilipin, adipocyte triacylglycerol lipase (ATGL) and hormone-sensitive lipase (HSL). Phosphorylation of perilipin modifies its barrier function, resulting in a restructuring of the surface of the lipid droplet and providing access of the lipases to the lipid droplets. The translocation of ATGL and HSL from cytosol to the lipid droplet results in the sequential hydrolysis of triacylglycerols (TAG) to diacylglycerols (DAG) then monoacylglycerols (MAG), which are hydrolysed by monoacylglycerol lipase (MAGL) producing non-esterified fatty acids (NEFA) and glycerol. Glycerol is directly released into the circulation; the NEFA are bound to adipocyte fatty acid binding protein (AFABP), which facilitates their intracellular trafficking from the droplet surface to the plasma membrane as part of their efflux from the cell. In plasma, NEFA circulate bound to other binding proteins (fatty acid binding proteins, FABP), of which albumin is the most abundant. Insulin also has many effects, most of which oppose the effects of the catecholamines. It stimulates lipoprotein lipase (LPL) activity increasing the hydrolysis of circulating TAG of TAG-rich lipoproteins (mainly VLDL) to facilitate the uptake of released NEFA, which are converted into TAG within the cell, and has an anti-lipolytic action by its activation on the phosphodiesterase activity, which converts cAMP into AMP. This mechanism reduces intracellular concentrations of cAMP, resulting in an inhibition of lipolysis. Conditions causing an insulin resistance, as is the case in late pregnancy, prevent these two effects of insulin, i.e. they decrease LPL activity and increase lipolytic activity. These actions are exaggerated at late pregnancy by the actions of catecholamines and other lipolytic hormones produced by the placenta.
ACS: acyl-CoA synthetase; MGAT: acyl-CoA monoacylglycerol acyltransferase; DGAT: acyl-CoA diacylglycerol acyltransferase.

Placental Transfer of Lipids

The placental transport mechanism for lipids is complex [9] and far from being understood. Essential fatty acids (EFA) and long-chain polyunsaturated fatty acids (LCPUFA) are needed for fetal growth and development, and must be transferred to the fetus from maternal circulation. The major proportion of those fatty acids are carried in maternal circulation in their esterified form associated with plasma lipoproteins, with only a minor proportion being in the form of NEFA [54, 55]. Lipoproteins in maternal plasma do not cross the placenta directly [9], but their fatty acids must be available to the fetus. The placenta has receptors for all the lipoproteins circulating in plasma, contains a number of different lipases (i.e. LPL, endothelial lipase, phospholipase A_2 and intracellular lipase) and different fatty acid binding proteins [9, 56-59]. Although the precise mechanism, by which these

components facilitate placental fatty acid transfer, is not completely understood, they do combine to allow both EFA and LCPUFA associated with plasma lipoproteins and those circulating as NEFA to be transferred to the fetus.

Cholesterol is an essential component of cell membranes, the precursor of bile acids and steroid hormones; it is required for cell proliferation, for the development of the growing body, for cell-to-cell communication and as precursor of regulatory agents. Consequently, embryonic and fetal cholesterol requirements are relatively high. During early gestation, maternal cholesterol actively contributes to fetal cholesterol, but during late pregnancy the main source appears to be fetal synthesis of cholesterol *de novo*. See ref. [9] for a review on the subject.

PREGNANCIES COMPLICATED BY INTRAUTERINE GROWTH RESTRICTION (IUGR)

IUGR is a condition associated with placental insufficiency as a result of shallow trophoblast invasion during the early stages of gestation [60]. During the third trimester of gestation, intrauterine growth of the fetus is accompanied by a large deposition of fat tissue [61]. Plasma fatty acid concentrations are normally higher in the mother than in the fetus. When IUGR fetuses were compared to fetuses of appropriate for gestational age (AGA) pregnancies, the fetal/maternal ratio was found to be higher for linoleic acid in the IUGR case and lower for both docosahexaenoic acid and arachidonic acid. These differences were interpreted as resulting from an inadequate transplacental supply of the acid or its precursor coupled to a lack of the fetal enzymes necessary for the synthesis of these fatty acids [62]. Indeed, a dysregulation of placental endothelial lipase and LPL, both enzymes involved in the supply of the acids, has been reported in IUGR pregnancies [63].

More recently, the concentrations in maternal plasma of lipophilic vitamins like retinol, γ - and α-tocopherol, of NEFA and of several individual fatty acids were found to be higher in women with IUGR than in AGA controls, but maternal plasma retinol and NEFA were the only variables that negatively correlated with birth and placental weights when multiple linear regressions were carried out [64]. These findings reflect an impaired placental transfer of lipophilic compounds in IUGR pregnancies. As retinoids are known to interact with nuclear receptors and can thereby modulate the transcription rates of genes including those involved in the regulation of cell proliferation and differentiation [65], it was proposed that the decrease in placental transfer of retinol could underpin the metabolic dysfunction found in IUGR pregnancies.

GESTATIONAL DIABETES MELLITUS (GDM)

Maternal Lipids and their Implications for Fetal Metabolism and Growth

Diabetic pregnancies are associated with a high incidence of fetal growth disorders. As well as the obvious disruptions to the control of glucose concentrations and metabolism in diabetes, there is evidence that disturbances in maternal lipid metabolism may also contribute to these disorders [13]. An altered lipid profile on the maternal side would affect the quantity and quality of lipids being transferred to the fetus. Hypertriacylglycerolemia in gestational diabetes mellitus has been related to a significant risk of having neonates that are large for gestational age [10], and circulating concentrations of TAG in the third trimester of pregnancy in diabetic women have been considered a stronger predictor of birth weight than glucose concentrations [10, 12].

When serum glucose concentrations were normal, maternal insulin, insulin resistance (homeostasis model assessment, HOMA) and glycerol values were found to be higher in women with GDM than in controls [12, 18]. In pregnant women with GDM, close to the time of delivery, maternal plasma TAG and NEFA concentrations correlated with all neonatal anthropometric measures (i.e. birth weight, body mass index (BMI) and fat mass). Furthermore, cord blood glucose, NEFA, insulin and HOMA were higher in GDM than in controls. In control pregnancies, maternal serum glucose, NEFA and glycerol concentrations all correlated with those in cord blood, but, unlike the case of NEFA in the women with GDM, not with neonatal weight and fat mass. In GDM, a negative correlation between cord blood TAG and neonatal weight or fat mass [12] was also found, whereas this relationship was not seen in controls where all fetal lipids showed a positive correlation with neonatal anthropometrics [18]. These findings show that in GDM, but not in controls, maternal lipids are strong predictors of fetal lipids and fetal growth. The similar concentrations of maternal lipids found in pregnancies with gestational diabetes and in control pregnancies but higher NEFA in the cord blood of those with GDM, are indicative of their more rapid placental transport or increased fetal adipose tissue lipolysis in GDM pregnancies as a result of decreased fetal insulin responsiveness [18].

Adipocyte Fatty Acid-binding Protein (AFABP) and Adipocytokines

Adipose tissue secretes several specific proteins called adipocytokines that play critical roles in energy homeostasis in adults; some of them also modulate insulin action in different tissues [66, 67]. On the basis of their known effects on both glycemic and lipid metabolism, and given the wealth of information on factors contributing to fetal growth, we focus here on the recently described adipocyte fatty acid-binding protein (AFABP) and three adipocytokines: leptin, adiponectin and retinol binding protein 4 (RBP4).

The AFABP have been described as being responsible for intracellular fatty acid trafficking that contributes to the regulation of the hormone-sensitive lipase (HSL) activity [68], which is one of the key enzymes controlling adipose tissue lipolysis (Fig. (**1**)). AFABP is present in human serum [69] and its concentrations are associated with insulin resistance and type 2 diabetes [69, 70]. In pregnant women it has been found that there are higher concentrations of AFABP in GDM than in control subjects, whereas they were lower in cord blood serum of GDM than in control subjects. AFABP concentrations in cord serum of control subjects were higher than in the corresponding maternal serum; this was not the case in GDM, even though the AFABP values in these GDM fetuses correlated with neonatal fat mass [17], indicating a direct interaction between the two.

It is well-known that leptin is produced by adipose tissue; it can also be secreted by other tissues, including the placenta [71], and during pregnancy its concentration in maternal plasma increases [72] as result of its secretion by both adipocytes and placental cells [71]. As well as increasing adipose tissue lipolysis, leptin modulates glucose metabolism and insulin sensitivity [73], and maternal hyperleptinemia could contribute to the availability of nutrients to the fetus. Leptin concentration in umbilical serum has a strong positive correlation with neonatal fat mass [74], and it is considered a marker of adiposity in the fetus. In GDM maternal plasma, leptin concentrations do not differ those in controls [17, 74], whereas higher concentrations of leptin have been found in fetal plasma and placentas from women with either type 1 diabetes or GDM compared to non-diabetic controls [75, 76]. Although the relationship between fetal leptin and birth weight have not been clearly established, higher concentrations of leptin in umbilical plasma leptin concentrations have been reported in diabetic pregnancies associated with fetal macrosomia [77-79]. In spite of these suggestive observations, there are not yet enough data to conclude that leptin acts as a direct determinant of fetal growth.

Retinol binding protein 4 (RBP4) is another adipocytokine. Apart from being involved in the mobilization and transport of retinol from liver to target tissues, it has also been shown to regulate glucose metabolism and insulin sensitivity [80]. The concentration of RBP4 in maternal plasma increases progressively with gestational age, probably because its synthesis increases as the placenta expands [81]. Its concentration in both maternal and cord blood serum is higher in GDM pregnant women than in controls [17, 82] and maternal values show a positive correlation with maternal fat mass [82]. Given that RBP4 is known to reduce insulin sensitivity [76], these findings indicate its contribution to the higher insulin resistance found in women with GDM and their newborns, although the implications for fetal growth and development remain unknown.

Unlike the foregoing adipocytokines, adiponectin increases insulin sensitivity. In adults its concentrations are inversely related to BMI and low concentrations are predictive of a risk for type 2 diabetes [83]. In human pregnancies, maternal adiponectin concentrations are lower in GDM than in control women [84], which could contribute to the higher insulin resistance found in the diabetic case. Adiponectin is synthesized in the placenta [85] as well as in several fetal tissues [86], which explains its high concentrations in umbilical plasma [87]. Cord blood adiponectin concentrations have been found to increase with gestational age and to correlate positively with birth weights [87], which indicate its possible role in fetal adiposity and development. In the GDM case however, cord blood adiponectin concentrations were lower than in controls and no relationship was found between this variable and neonatal fat mass or birth weight [88].

As well as the adipocytokines discussed above, there are several others which affect lipid metabolism either directly or indirectly. Potentially they all could affect fetal growth in both normal and diabetic pregnancies, although the nature and significance of their involvement remain to be investigated.

The Effects of Placental LPL Activity and Angiopoietin-like 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 [13, 89]. 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 [90, 91]. 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 [30, 92].

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 [93]; conversely, there was a reduction of placental LPL activity in pregnancies complicated by intrauterine growth restriction [94], which is normally characterized by reduced fetal fat depots [95]. 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 [94, 96].

The activity of some lipases is regulated by the action of members of the angiopoietin-like (ANGPTL) protein family [97-99]. One of these proteins, ANGPTL4, is secreted into the blood from adipose tissue, liver and placenta [100] and has been shown to inhibit LPL activity irreversibly by converting active LPL dimers into inactive monomers [101, 102]. As hypertriacylglycerolemia and tissue-specific changes in LPL activity are routinely found during late pregnancy [31], 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 [7]. 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 being 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 [7].

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 [7].

FINAL CONSIDERATIONS AND CONCLUSIONS

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.

The active and efficient involvement of lipid metabolism during pregnancy on fetal fat mass and growth is clearly shown by the consequences of its being disrupted in pathological conditions. Intrauterine growth restriction has been associated with impaired placental transfer of lipophilic compounds, including not only fatty acids but also lipophilic vitamins like retinol and γ - and α-tocopherol. Gestational diabetes mellitus is normally associated with disturbances in maternal lipid metabolism even when serum glucose concentrations are normal. As well as changes in serum TAG, NEFA and lipoprotein profiles, alterations in the concentrations of different adipocytokines and other proteins like ANGPTL in maternal circulation occur in pregnant GDM women, indicating an unbalanced lipid metabolism. Although these disturbances imply major effects of lipid metabolism on fetal adiposity and growth, a detailed understanding of the precise mechanisms involved remains to be established.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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