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REVIEW

# Placental fatty acid transport in maternal obesity

**I. Cetin[1]*, F. Parisi[1], C. Berti[1], C. Mandò[1] and G. Desoye[2]**

[1]*Department of Clinical Sciences L. Sacco, Unit of Obstetrics and Gynecology, University of Milan, Milano, Italy*
[2]*Department of Obstetrics and Gynaecology, Medical University of Graz, Graz, Austria*

Pregestational obesity is a significant risk factor for adverse pregnancy outcomes. Maternal obesity is associated with a specific proinflammatory, endocrine and metabolic phenotype that may lead to higher supply of nutrients to the feto-placental unit and to excessive fetal fat accumulation. In particular, obesity may influence placental fatty acid (FA) transport in several ways, leading to increased diffusion driving force across the placenta, and to altered placental development, size and exchange surface area. Animal models show that maternal obesity is associated with increased expression of specific FA carriers and inflammatory signaling molecules in placental cotyledonary tissue, resulting in enhanced lipid transfer across the placenta, dislipidemia, fat accumulation and possibly altered development in fetuses. Cell culture experiments confirmed that inflammatory molecules, adipokines and FA, all significantly altered in obesity, are important regulators of placental lipid exchange. Expression studies in placentas of obese–diabetic women found a significant increase in FA binding protein-4 expression and in cellular triglyceride content, resulting in increased triglyceride cord blood concentrations. The expression and activity of carriers involved in placental lipid transport are influenced by the endocrine, inflammatory and metabolic milieu of obesity, and further studies are needed to elucidate the strong association between maternal obesity and fetal overgrowth.

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**Key words:** fatty acids, maternal obesity, placental transport, pregnancy

## Introduction

Consistent with the rising incidence of obesity, there has been a two-fold rise in women identified as obese during pregnancy[1,2] and over 40% of mothers at term exceed the Institute of Medicine Guidelines for optimal weight gain during pregnancy.[3] Maternal pregestational obesity is a significant risk factor for adverse outcomes during pregnancy, leading to increased morbidity and mortality of mother and child[4,5] and to increased demands on health services.[6] In particular, obesity is an important independent risk factor for developing hypertensive disorders and gestational diabetes mellitus (GDM), with a three times higher risk compared with non-obese mothers.[7–9] Moreover, the offspring of obese women are two to four times more likely to be large for gestational age (birth weight >90th centile for gender, ethnicity, parity and gestation) or macrosomic (birth weight >4 kg) than the offspring of their lean counterparts with the ensuing higher risk for maternal and fetal trauma and interventions during labor.[10]

Maternal obesity is associated with a specific proinflammatory and metabolic phenotype, which may lead to increased supply of nutrients to the feto-placental unit.[11–13] However, also placental function and transport may be directly affected by the obese environment.[14,15]

*Address for correspondence: Prof. I. Cetin, Department of Clinical Sciences L. Sacco, Unit of Obstetrics and Gynecology, University of Milan, via GB Grassi 74, 20157 Milan, Italy.
(Email irene.cetin@unimi.it)

As the phenotype of an individual can be driven by nutrition *in utero* and as appropriate fetal growth can be achieved only with an adequate interaction between mother, placenta and fetus,[16,17] maternal obesity may represent an important prenatal risk factor for the adult metabolic syndrome.[18] A mixture of nutrients contributes to fetal growth and development. However, the relative contribution of each individual component awaits investigation. This review focuses on fatty acids and summarizes the current knowledge about their transport across the placenta in human maternal obesity. As obesity is often associated with insulin resistance, we have also considered studies that associate obesity to GDM. In some cases also animal studies are included in relation to specific pathogenic mechanisms.

## Maternal supply of lipids to the placenta

Fatty acids (FAs), together with glucose, lactate, cholesterol and amino acids, represent essential nutrients for adequate fetal growth. The recommended daily fat intake for adults, mostly introduced as triglycerides, ranges between 20% and 35% of total calories (US recommendations).[19] Although dietary fat intake in pregnancy should be the same as for the general population, it has been recently recommended that pregnant and lactating women should aim at achieving an average intake of at least 200 mg/day of ω-3 FA, in order to improve pregnancy and neonatal outcomes (Perilip Consensus Conference).[20] In particular, an adequate intake of docosahexaenoic acid (DHA) has been emphasized in order

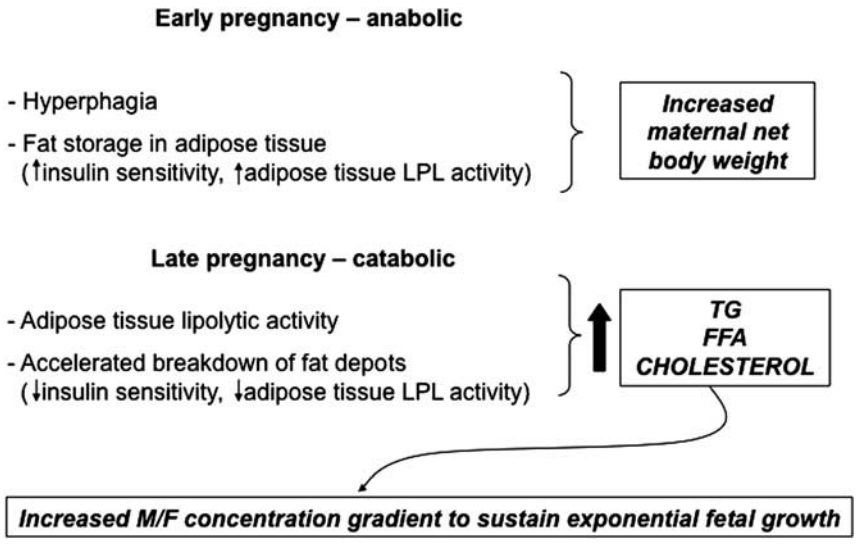


**Fig. 1.** Changes in maternal metabolism of dietary fats during pregnancy. Pregnancy is a dynamic state, during which adjustments in nutrient metabolism evolve continuously as the mother switches from an anabolic condition during early pregnancy to a catabolic state during late pregnancy. Lipid metabolism switches from fat deposition due to both hyperphagia and enhanced lipogenesis during early pregnancy to fat breakdown during late pregnancy.[22–24] LPL, lipoprotein lipase; FFAs, free fatty acids.

to sustain proper development of the fetal retina and brain. Thus, it is recommended to eat oily fish twice a week. The supply of lipids is particularly important in order to ensure a proper development and growth to the fetus.[21] The mother modifies her metabolism from the beginning of pregnancy in order to support the nutritional needs of the feto-placental unit by increasing maternal serum lipid concentrations.[22,23] The early part of pregnancy is considered as an anabolic period characterized by hyperphagia and fat storage in adipose tissue, resulting in increased maternal net body weight (Fig. 1).[23,24] This period is relevant in order to determine adequate maternal lipid availability not only later in gestation, but even in lactation, when the increased lipolytic activity leads to the augmentation of circulating lipids to sustain neonatal growth.

Maternal plasma-free fatty acid (FFA) levels double at delivery in normal pregnancies.[25] In particular, the proportion of saturated FA increases with gestation, with higher proportions in cord blood plasma, whereas ω-6 FA declines, with only arachidonic acid (ARA) enhanced in umbilical blood. The proportion of ω-3 FA is stable during pregnancy. Also, cholesterol and triglyceride levels significantly increase during pregnancy, mostly near delivery.[25]

### *Effects of obesity on maternal lipid metabolism*

Obesity may lead to fetal overgrowth through different mechanisms that can be schematized in increased maternal nutrient availability to the fetus and changes in placental transfer capacity.

Adipose tissue is now recognized not simply as a store of excess energy but as a major endocrine and secretory organ.[26,27] It is largely accepted that fat cells secrete adipokines, which likely contribute to the endocrine derangements that characterize obesity.[28]

Physiological insulin resistance is increased in obese women without GDM and peripheral insulin sensitivity is about 40% lower compared with non-obese mothers.[29,30] These effects can be explained by a significant reduction of insulin receptor substrate-1 protein levels in the adipose tissue of obese women with GDM compared with controls.[31] When the metabolic environment of obese compared with non-obese women in late pregnancy was evaluated, the obese group showed more cases of dislipidemia with high levels of triglycerides and low concentrations of high-density lipoproteins, significant hyperleptinemia and hyperinsulinemia and elevated levels of inflammatory molecules such as interleukin-6 and sensitive C-reactive protein.[32] Metabolic alterations in obese pregnancies independent of diabetes were also recently confirmed, demonstrating in particular that obese mothers without diabetes, despite a controlled diet, have higher daytime and nocturnal glucose profiles than normal-weight women. In this study, body fat in infants was strongly related to maternal plasma nutrient concentrations, with triglycerides as the major predictors of excess fetal growth.[33]

Maternal obesity is therefore associated with changes in the maternal lipid profile reaching the placenta, that is, increased triglycerides and decreased levels of high-density lipoproteins, as well as with a proinflammatory state. All these changes may account for placental inflammation associated with maternal obesity.[34–36] However, no data are available on changes in long-chain polyunsaturated fatty acids (LC-PUFAs) profile in obese pregnant women. Maternal lipids are strong predictors of fetal growth, suggesting that placental lipid transfer is fundamental in fetal overgrowth.

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## Placental FA transfer

The placenta is the key regulator of fetal growth because of its role in nutrient and metabolic waste transport and its endocrine function.[37,38] Determinants of placental nutrient transfer capacity are nutrient concentration gradients, placental morphology, utero- and feto-placental blood flows and efficiency of specific transport mechanisms.[37,38] Changes in the rate of placental nutrient delivery may cause altered fetal growth.[38]

A small proportion (1–3%) of PUFA may be found in the maternal circulation directly in their free non-esterified form (FFA), whereas the bulk of FA circulates as triglycerides, phospholipids and cholesterol esters in complex lipoproteins.[13,39] Thus, prior to their placental uptake these lipids have to bind to the lipoprotein receptor located in the microvillous membrane adjacent to placental lipases. This leads to hydrolysis and results in the release of FFAs for uptake by the syncytiotrophoblast.[40] FFAs are transferred to the fetus across the placenta through a saturable, protein-mediated mechanism probably involving transport proteins located on trophoblast and on endothelial cells of fetal capillaries.[40] Indeed, several FA transfer proteins have been identified: FABP-pm (FA binding protein-plasma membrane), located only on the maternal side of trophoblast cells and preferentially binding LC-PUFA; FABP-L (liver-FABP) found in cytoplasm; FAT/CD36 (FA translocase) and FATPs (FA transporter proteins), integral transmembrane proteins located on both trophoblast membranes (Fig. 2).[41] Once inside the cytoplasm FFAs are bound to FABPs and follow various pathways: FFAs are partly oxidized to produce energy, partly used as structural components in placental lipids and to form prostaglandins, partly re-esterified to form triglycerides, phospholipids and cholesterol esters; the remaining FFAs are elongated, desaturated and then released through the basal membrane into the fetal circulation.

Perilipins, also referred to as adipophilins, are lipid droplet-associated proteins expressed in human placentas and involved in processes of lipid storage and homeostasis, cell signaling and vesicle trafficking.[42] Lipid droplet formation is enhanced *in vitro* in cultured trophoblast cells exposed to FA combined with insulin, demonstrating that trophoblast is capable of packaging lipids for further storage.[43] Lipid droplets can also be found *in vivo* mostly in the syncytiotrophoblast.[44] Interestingly, hypoxia and peroxisome proliferator-activated receptor (PPAR) agonists increase *in vitro* the expression of selected FABP and FATP with a marked increase in lipid droplet accumulation in trophoblast, suggesting that these proteins likely play a role in placental lipid uptake, metabolism and storage.[45]

Placental transfer ultimately provides the fetal mix of FA. In normal pregnancies fetal FA, despite being strictly dependent on maternal levels, are significantly lower than in maternal plasma (fetal/maternal concentration ratio: 1/3).[46] Also, the FA profile appears to be different in the fetal circulation, a phenomenon called 'biomagnification'. It is characterized by higher proportions of the LC-PUFA derivatives ARA and DHA, and lower percentages of their precursors, linoleic (LA) and α-linolenic (α-LA) acids, in fetal compared with maternal plasma.[47] Although the fetus is able to synthesize DHA and ARA, the role of synthesis seems to be low so that biomagnification is probably due to the placental

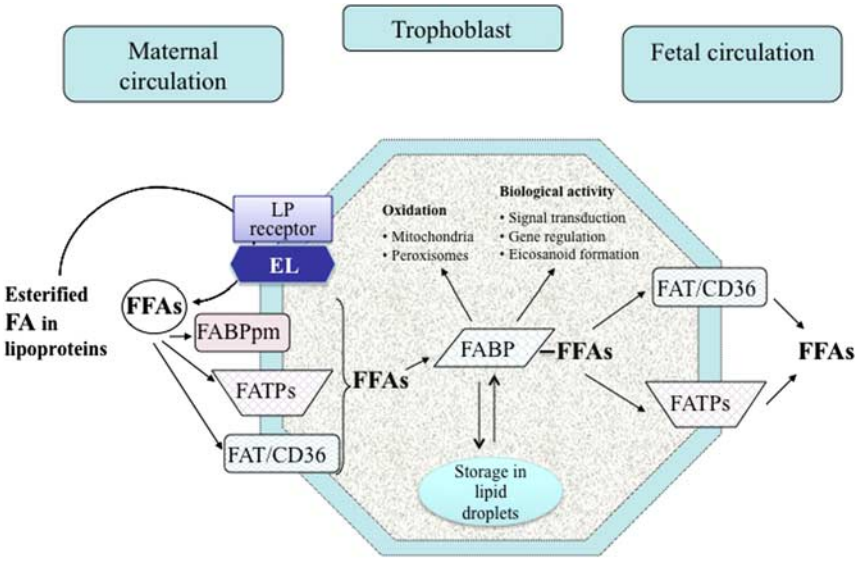


**Fig. 2.** Scheme of putative lipid handling in the human placenta. The mechanisms and molecules involved in lipid release from the syncytiotrophoblast have remained elusive. FA, fatty acid; FFAs, free fatty acids; FABPpm, FA binding protein-plasma membrane; FAT/CD36, FA translocase; FABP-L, liver FABP; FATPs, FA transporter proteins; EL, lipase – these include endothelial lipase and possibly further yet unidentified lipases; LP receptor, lipoprotein receptor.

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ability to preferentially transfer DHA and ARA into fetal circulation as demonstrated by *in vivo* studies and by stable isotope experiments.[48,49]

### *Placental FA transfer in maternal obesity*

Placental surface, thickness and size are related to maternal fat mass and body mass index.[50,51] Thus, in obese women placental size and, hence, surface area of exchange may be enlarged and facilitates maternal–fetal exchange. The role of adipokines in stimulating or inhibiting placental cell cycle is not known, however, their increased levels in maternal obesity may contribute to placental structural changes. Interestingly, leptin (known to be increased in maternal obesity) is protective against trophoblastic apoptosis and has been reported to promote trophoblast proliferation.[52] Maternal and fetal blood flows are further regulators of placental exchanges as they influence flow-limited transport.[53] However, no data are available on vascular development and architecture in the feto-placental unit of obese women. It may be hypothesized that the wide range of proinflammatory signals produced in obese mothers might play a role in a possibly altered placental vascular function, which may contribute to explain the higher risk of preeclampsia and fetal growth restriction in these women.

Other important key variables determining transplacental transport are represented by the efficiency of specific transport mechanisms, that is, number, density, distribution and activity of carrier proteins. For FA, another level of regulation is represented by the activity of the lipases, which hydrolyse lipoprotein-borne triglycerides to release FFA for subsequent uptake. It is currently unclear which of these mechanistic steps is rate limiting for FA transport.

Specific alterations have been described in the expression of FA placental transfer in GDM. L-FABP is increased in GDM compared with controls,[54] whereas placental lipoprotein lipase (LPL) activity has been found to be increased by 39% in Type 1 Diabetes Mellitus but not in GDM patients. We reported that, while FA levels in venous cord plasma did not differ between GDM and control neonates, a lower percentage of DHA, ARA, ω-3 and ω-6 PUFA was found in umbilical arterial plasma.[55] These data suggest that the lower proportions of LC-PUFA in neonates of GDM mothers seem to be due to altered fetal metabolism, likely due to the anabolic effect of fetal hyperinsulinism, rather than limited placental transfer.

Few studies are available on a possible placental phenotype for FA transport proteins associated with maternal obesity. Currently, available data are obtained from animal models, primary human trophoblast culture and expression studies in human placentas.

In a recent obese animal model of periconceptional high fat diet, fetuses of obese ewes had increased blood concentrations of cholesterol, triglycerides and FFA and augmented FATP1, FATP4 and FAT gene and protein cotyledonary expression at midgestation compared with fetuses of non-obese ewes. Placental LPLs expression was similar in both groups, probably indicating that the difference in fetal FFA concentrations was due to different placental transport mechanisms and not due to triglyceride hydrolysis. PPAR, known to regulate the expression of FATPs and placental lipid storage, was increased in the obese group.[56] In the same model, obese ewes presented significantly increased expression of inflammatory signaling molecules in placental cotyledonary tissue at midgestation. In particular, maternal obesity increased FFA in fetal circulation, which activated Toll-like receptor (TLR)-4 signaling and inflammatory signaling pathways, involving nuclear factor kappa B (NF-kB) and Jun N-terminal kinase (JNK). As a result, the expression of inflammatory cytokines was increased. Placental inflammation may induce systemic fetal inflammation, thereby negatively affecting fetal development.[57]

In diabetic and obese pregnant women, the expression of endothelial lipase (EL), the predominant triglyceride-lipase family member in the human placenta, is significantly upregulated only in mothers who are obese and diabetic as compared with lean pregnancies, whereas diabetes or obesity alone have no significant effect.[58]

In cell culture experiments, tumour necrosis factor (TNF)-α and leptin, but not glucose or insulin, were identified as regulators of EL expression.[58] This may suggest that a certain level of inflammation in the mother, placenta or fetus is needed to induce the molecular changes and trophoblast FA accumulation.[59] Differently, an increase in LPL activity has been shown after incubation with hyperglycemic medium plus insulin.[60]

However, not all lipid regulating molecules are governed by inflammation. Phospholipid transfer protein is upregulated in the placenta of GDM women independent of maternal obesity.[61] This notion is also supported by a reported 20–40-fold increase in FABP4 expression and a four-fold increase in cellular triglyceride content in placentas of obese–diabetic women but not in obesity alone.[43] This was also associated with a significant increase in triglyceride cord blood concentrations in neonates born from obese–diabetic mothers. In the same study, FABP4 expression was markedly augmented in cell cultures exposed to FA, but not to insulin. Moreover, the reduced trophoblast triglyceride content after FABP4 inhibition suggests that FABP4 is essential for trophoblast lipid accumulation.[43]

## Conclusions

Maternal obesity alone seems to markedly upregulate inflammatory signaling pathways and is associated with augmented fetal lipid levels in the fetus, possibly not only because of changes in maternal lipid levels but also because of altered placental transport mechanisms. The expression and activity of carriers implicated in lipid transport at the maternal–fetal interface is influenced by the endocrine, inflammatory and metabolic milieu of obesity. However, some of them appear altered only by the association of obesity with GDM. As the mechanisms underlying placental lipid transport are not

understood, there is a call for further studies that may elucidate the strong association between maternal obesity, alterations in placental lipid transport and fetal overgrowth. A key question that has not been resolved to date is: which are the rate limiting steps that regulate placental lipid exchange? Several potential mechanisms need to be investigated: hydrolysis of triglycerides and phospholipids by endothelial or other yet to be identified lipases; transport across the microvillous and/or the basal membrane; transfer across the trophoblast cytoplasm; re-esterification within the placenta and in the fetal circulation; contribution of different cell types such as endothelial cells besides trophoblast cells. Moreover, the capacity of the placenta to transport FA is unknown as well as the proportion of FA taken up by the syncytiotrophoblast, which is used for placental metabolism. The extent and regulation of lipid storage in the placenta is unknown and it is also unclear if the lipids stored in lipid bodies can be mobilized to ultimately contribute to the cytoplasmic FA pool.

A key question seems to be whether the placenta limits the transfer of FA at all, or if the transfer is more dictated by the maternal to fetal gradient similar as for glucose. If the concentration gradient is the driving factor, then fetal insulin may be a potent driver by its ability to regulate anabolic processes in the fetus and, thus, uptake into and sequestration of FA in fetal tissues. All these questions await an answer.

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