

## Role of Insulin and Glucose in Fetal Fat Mass Development

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Under healthy conditions, fetal development is greatly influenced by the nutrients crossing the placenta which depends on maternal dietary and metabolic conditions. Glucose is the compound crossing the placenta in greatest quantities and there is a positive correlation between maternal serum glucose concentrations and neonatal body weight or fat mass [1]. However, maternal hyperlipidemia (mainly hypertriglyceridemia [2]) and fat depots accumulation are characteristic features during the last third of gestation and although lipids cross the placenta with difficulty [3], during the last 10 weeks of gestation until term it has been shown that in newborn infants the proportion of body weight present as fat increases linearly with gestational age [4,5]. In comparison to all mammalian species humans are born with one of the highest percentages of body fat and several factors seem to contribute to such rapid development of fetal fat mass during late gestation. De novo synthesis of fatty acids is active in the human fetus from the 28th week of gestation [6] and besides several regulatory factors that includes its activation by insulin, it depends on the substrate availability of which glucose is its main component. Maternal glucose reaching the fetus as result of the maternal/fetal gradient would be used by fetal liver to facilitate lipogenesis. Synthesized fatty acids are pooled with those non-esterified fatty acids (NEFA) reaching the fetus from the mother. Polyunsaturated fatty acids (PUFA) are needed to sustain fetal growth [7] and most of them are carried in maternal blood in their esterified form associated to different lipoproteins that are recognized by specific lipoprotein receptors present in the placental trophoblast cells. After their hydrolysis by the action of placental endothelial lipase and lipoprotein lipase (LPL) the fatty acids are released to fetal circulation in the form of NEFA and it has been shown that placental LPL activity positively correlate with newborn adiposity [8]. In the fetus the liver is not functionally developed [9] but in adults fatty acids are esterified in liver for the TAG synthesis and are released into circulation associated to VLDL. Extrahepatic LPL in concert with hepatic lipase (HL) and cholesteryl ester transfer protein (CETP) hydrolyze TAG in VLDL and these lipoproteins are first converted to smaller intermediate-density lipoproteins (IDL) and finally to low-density lipoproteins (LDL) [10]. The process is not completely known in the fetus, but the activity and mass of CETP in cord blood was found higher than in adults [11]. Besides, by studying post-heparin plasma it has been shown that whereas LPL activity is similar in full-term newborns and adults, the activity of HL is even higher in cord blood than in adults [12] and based in the increase of both NEFA and glycerol in vitro in the presence of heparin found in homogenates of adipose tissue from human fetus of 13 - 18 weeks of intrauterine life [13] it can be concluded that LPL is present in fetal adipose tissue. This would facilitate the hydrolysis of circulating lipoprotein triacylglycerols (TAG) and after the uptake of their lipolytic products they are re-esterified intracellularly to form TAG for accumulation within the tissue, actively contributing to fetal fat deposition. Regulation of LPL activity is tissue specific and carried out by different factors. In adipose tissue insulin is a major positive regulator of LPL activity [14] and glucose also increases its activity [15] whereas angiopoietin-like proteins 3 and 4 (ANGPTL) are inhibitors [16]. However, in newborns of women with well-controlled gestational diabetes mellitus with high fat mass in comparison with controls it was found higher concentrations of ANGPTL4 [17]. Those newborns have increased serum insulin and glucose levels [1] and it is therefore proposed that such LPL inhibitory effect of ANGPTL4 could be overcome by their hyperinsulinemia and hyperglycemia.

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