Review Article

Annals of Nutrition & Metabolism

Ann Nutr Metab 2017;70:228–231
DOI: 10.1159/000463397

Received: February 1, 2017
Accepted: February 13, 2017
Published online: March 17, 2017

Placental Lipid and Fatty Acid Transfer in Maternal Overnutrition

Rohan M. Lewis[a] Gernot Desoye[b]

[a]Faculty of Medicine, University of Southampton, Southampton, UK; [b]Department of Obstetrics and Gynaecology, Medical University of Graz, Graz, Austria

Keywords
Obesity · Transport · Metabolism · Trophoblast · Lifelong health

Abstract
Background: The increasing incidence of childhood obesity is a significant public health challenge, the consequences of which extend across the life course. ***Summary:*** Diet and exercise are clearly the major contributors to childhood obesity, but the factors predisposing to obesity may become established in the womb. Worryingly maternal overnutrition, in particular when it leads to obesity and diabetes, perpetuate an intergenerational cycle of obesity through its effects on placental function and fetal metabolism. This review will address the ways in which the placental lipid and fatty acid transfer may lay the foundations for obesity in the context of maternal overnutrition. ***Key Messages:*** (1) Metabolic changes associated with maternal obesity affect placental nutrient handling. (2) Altered placental nutrient handling may induce pro-adipogenic changes in the fetus, in particular increased fetal insulin. (3) Understanding the effects of maternal obesity on the placenta will aid the development of effective interventions to optimise pregnancy outcomes.

Since the WHO declared obesity as a worldwide epidemic in 2003, attention has focused on understanding, among other things, the pathophysiological and molecular mechanisms underlying this condition. Especially alarming is the fact that in Europe at least 20% of the children at the age of 10 years are already overweight or obese. Childhood obesity is accompanied with a higher number of adipocytes, which can store excess energy in the form of triglycerides. Epidemiological studies have established high birth weight and in particular excessive neonatal adiposity as important risk factors for childhood obesity. The Developmental Origins of Health and Disease concept posits that the roots of obesity, or a predisposition to obesity, are established in utero [1].

Based on the hyperglycemia/hyperinsulinemia concept of Pedersen and Osler [2], expanded on by Freinkel [3], maternal overnutrition results in fetal oversupply of the main building blocks for triglycerides, that is, glucose and fatty acids. Placental glucose transfer is driven by the transplacental gradient, and high maternal glucose will increase the fetal glucose and stimulate fetal insulin release [4]. Insulin is a key driver for hepatic fatty acid and triglyceride synthesis in white adipose tissue, and both the availability of fatty acids and the hyperinsulinemic environment may promote fetal adiposity. This may lead to fetal overgrowth, primarily due to increased adiposity,

KARGER

E-Mail karger@karger.com
www.karger.com/anm

Prof. Gernot Desoye
Department of Obstetrics and Gynaecology
Medical University of Graz
Auenbruggerplatz 14, AT–8036 Graz (Austria)
E-Mail gernot.desoye@medunigraz

and the birth of a large for gestational age baby. Being born large for gestational age is associated with increased risk of obesity and diabetes in later life.

The role of fatty acids and their supply through the placenta in the context of maternal overnutrition is of growing interest. Early studies have demonstrated that the fatty acid composition of fetal fat was similar to that of the mother until around week 26–28 of gestation [5]. This suggested that maternal fatty acids are used for the synthesis of triglycerides in the fetus for their storage in fetal adipocytes, but their relative contribution to fetal fat depots at that stage in pregnancy is unknown. This is different at the end of gestation when the fatty acid composition of neonatal fat differs from that of the mother [5]. Fetal hepatic synthesis of fatty acids from glucose may explain this change in the composition of the fetal fatty acids pool. However, selective placental transfer or metabolism of fatty acids could also contribute to the maternal fetal difference in fatty acid composition in the latter part of gestation. In diabetic pregnancies, the fetal plasma fatty acid profile in the venous cord blood leaving the placenta does not significantly differ from those of non-diabetic pregnancies. However, in the arterial cord blood from diabetic pregnancies, the proportion of polyunsaturated fatty acids is reduced [6]. This may suggest increased fetal utilisation of these fatty acids in gestational diabetes mellitus.

Support for the notion of the fetal rather than maternal origin of fetal fatty acids comes from ex vivo placental perfusion studies, which show an inefficient maternal-fetal transfer of fatty acids at the end of gestation. Only about 2–4% of the fatty acids in the maternal circulation are transferred to the fetus at any given time [7]. Stable isotope studies administering ^{13}C-fatty acids to mothers 12 h prior to caesarean section [8] also found a low level of tracer enrichment in the fetal umbilical cord blood. This enrichment was slightly higher for DHA (C22:6) than for other fatty acids tested (C16:0, C18:1, C18:2) [9]. Importantly, the enrichment of most fatty acids was unchanged in gestational diabetes mellitus except for DHA, which was lower [8].

Fatty acid transporters on the microvillus of the syncytiotrophoblast membrane account for fatty acid uptake into the trophoblast. After crossing the plasma membrane, the fatty acids will be ligated with coenzyme-A resulting in the formation of acyl-CoA species. This acyl-CoA can enter the metabolic pool to (a) become re-esterified for storage in lipid droplets or other lipid pools such as phospholipid, (b) become oxidised, or (c) converted into eicosanoids or other fatty acid derivatives. Both uptake of fatty acids from the mother and their release from intraplacental lipid pools may, in principle, provide fatty acids for delivery to the fetus. Placental metabolism may be involved in determining the proportion of placental fatty acids being released for fetal supply [10]. Alternatively, a proportion of fatty acid transfer across the placenta may be independent of transporters and metabolism, but involves simple diffusion of fatty acids driven by the maternal-fetal concentration gradient.

One has to keep in mind that both the in vivo stable isotope studies and the ex vivo placental perfusion studies administered free fatty acids. However, the vast majority (~97% [11]) of circulating fatty acids is esterified and packaged into lipoproteins. Before their uptake into the syncytiotrophoblast, the fatty acids have to be released by lipolysis, most likely by endothelial lipase [12]. The enzyme is stably expressed and not affected by maternal gestational diabetes or obesity. Only when obesity is superimposed by gestational diabetes, the endothelial lipase is upregulated [13]. Thus, there seems to be a threshold above which endothelial lipase expression is changed. This threshold may be established by circulating concentrations of pro-inflammatory cytokines such as tumour necrosis factor-alpha [13].

An open question is whether the small proportion (~3% [11]) of maternal fatty acids that circulate in their free form is sufficient for an adequate fatty acid supply to the fetus. It is likely that a certain proportion of fatty acids destined for transfer to the fetus is derived through lipolysis by endothelial lipase on the syncytiotrophoblast surface. If so, then it also remains to be determined whether endothelial lipase activity may represent the rate-limiting step, especially under conditions of gestational diabetes in obese women. Experiments using labelled fatty acids and lipoproteins containing labelled triglyceride are required to address this issue.

The vast majority of placental fatty acids must be derived from the mother rather than de novo synthesised in the placenta from glucose or acetate. There is little interaction in the human syncytiotrophoblast between glucose and fatty acid metabolic pathways [14, 15]. Under normal, non-diabetic conditions and in lean women, only about 3% of maternal glucose is converted into fatty acids in triglycerides and about 10% of the glucose taken up contributes to the supply of glycerol as triglyceride precursor [14].

DHA is an essential fatty acid for the fetus, and efficient transplacental transfer mechanisms are, therefore, vital for adequate fetal development, in particular, for the brain and retina. In addition to broad spectrum fatty acid transporters, the placenta expresses DHA-specific transporter protein [16]. The expression of this transporter is reduced in gestational diabetes mellitus and may be involved in

limiting transplacental DHA transfer in this condition. Details about the placental DHA transfer mechanisms and their molecular and functional regulation under various maternal conditions have remained elusive. However, DHA uptake into the syncytiotrophoblast appears reduced in gestational diabetes, which may affect its supply to the fetus and fetal neurodevelopment [17].

Maternal obesity is associated with a lipotoxic placental environment with activation of pathways involved in both inflammation and oxidative stress [18]. Maternal obesity has also been shown to modulate intracellular lipid turnover in the human term placenta by the up-regulation of CGI-58, a key regulator of TG hydrolysis [19]. These changes in the placenta may be mediated by exposure to elevated lipid levels in the maternal circulation or the pro-inflammatory cytokine environment associated with obesity. The ability of the placenta to store fatty acids may be important in minimising any lipotoxicity due to increased exposure.

It is well known that the placenta stores fatty acids after their esterification into triglycerides in the form of lipid droplets, primarily in the syncytiotrophoblast. Storage of triglyceride is higher in maternal diabetes and obesity, both conditions associated with elevated circulating levels of triglycerides and fatty acids in the mother [20]. The main drivers for fatty acid storage and lipid droplet formation are fatty acids [15] and insulin [19]. This explains the elevated placental triglyceride storage in maternal diabetes and obesity when both fatty acid and insulin levels are increased. However, the trophoblast capacity to store fatty acids is limited, because, with increasing degrees of obesity and the associated increases in fatty acid and insulin levels, placental triglyceride levels do not rise further. This levelling off may be the result of triglyceride mobilisation through the activation of CGI-58, a co-activator of adipose tissue triglyceride lipase, due to maternal hyperinsulinemia [21]. At some level of maternal hyperinsulinemia, lipogenesis and lipolysis in the trophoblast may be in a dynamic balance, ultimately resulting in unaltered net triglyceride levels.

Whether the free fatty acids derived from the trophoblast lipid droplets by lipolysis enter other metabolic pathways such as fatty acids oxidation, are converted into eicosanoids or are released into the maternal or fetal circulation is unknown. It is pertinent that placental explants from gestational diabetes mellitus exhibited a 40–50% reduced capacity for fatty acid oxidation compared to control placentas [22]. This may lead to increased delivery to the fetus or push these fatty acids into other lipid pools.

It is also important to consider potential sex differences in placental metabolism and transport of fatty acids. Fatty acid uptake into the syncytiotrophoblast is lower for oleic acid in male placentas [23]. Maternal dietary supplementation with n-3 fatty acids has sexually dimorphic effects on the placental transcriptome, with female placentas being more responsive to treatment [24]. Such differences may influence or confound the outcome of the studies, and the sex of the placenta needs to be taken into account in future work.

Conclusion and Perspectives

The metabolic changes associated with maternal obesity and diabetes affect the placental transfer of nutrients and metabolic status in the fetus. In particular, high fetal insulin may drive metabolic pro-adipogenic changes that predispose to increased fetal fat deposition, higher birth weight and postnatal adiposity. Further work is required to understand the metabolism of nutrients by the placenta and how this is altered by changes in maternal metabolism and how it may be different in male and female fetuses. The incorporation of fatty acids into placental triglycerides stored within lipid droplets is one important pathway within the placenta. However, fatty acids may also enter other esterified lipid pools, including phospholipid and cholesteryl esters and future work needs to delineate these pathways. Understanding these processes will support the development of effective interventions to optimise maternal metabolism, placental function and the lifelong health of the offspring.

Acknowledgements

This research was funded by the European Union's Seventh Framework Programme (FP7/2007-2013), project EarlyNutrition under grant agreement No. 289346.

Disclosure Statement

The authors have no conflicts of interest.

References

1 Lewis RM, Demmelmair H, Gaillard R, Godfrey KM, Hauguel-de Mouzon S, Huppertz B, Larque E, Saffery R, Symonds ME, Desoye G: The placental exposome: placental determinants of fetal adiposity and postnatal body composition. Ann Nutr Metab 2013;63:208–215.
2 Pedersen J, Osler M: Hyperglycemia as the cause of characteristic features of the foetus and newborn of diabetic mothers. Dan Med Bull 1961;8:78–83.

3 Freinkel N: Banting lecture 1980. Of pregnancy and progeny. Diabetes 1980;29:1023–1035.
4 Day PE, Cleal JK, Lofthouse EM, Hanson MA, Lewis RM: What factors determine placental glucose transfer kinetics? Placenta 2013;34:953–958.
5 Hirsch J, Farquhar JW, Ahrens EH Jr, Peterson ML, Stoffel W: Studies of adipose tissue in man. A microtechnic for sampling and analysis. Am J Clin Nutr 1960;8:499–511.
6 Ortega-Senovilla H, Alvino G, Taricco E, Cetin I, Herrera E: Gestational diabetes mellitus upsets the proportion of fatty acids in umbilical arterial but not venous plasma. Diabetes Care 2009;32:120–122.
7 Dancis J, Jansen V, Kayden HJ, Schneider H, Levitz M: Transfer across perfused human placenta. II. Free fatty acids. Pediatr Res 1973;7:192–197.
8 Gil-Sanchez A, Larque E, Demmelmair H, Acien MI, Faber FL, Parrilla JJ, Koletzko B: Maternal-fetal in vivo transfer of [13c]docosahexaenoic and other fatty acids across the human placenta 12 h after maternal oral intake. Am J Clin Nutr 2010;92:115–122.
9 Pagan A, Prieto-Sanchez MT, Blanco-Carnero JE, Gil-Sanchez A, Parrilla JJ, Demmelmair H, Koletzko B, Larque E: Materno-fetal transfer of docosahexaenoic acid is impaired by gestational diabetes mellitus. Am J Physiol Endocrinol Metab 2013;305:E826–E833.
10 Perazzolo S, Hirschmugl B, Wadsack C, Desoye G, Lewis RM, Sengers BG: The influence of placental metabolism on fatty acid transfer to the fetus. J Lipid Res 2017;58:443–454.
11 Herrera E, Desoye G: Maternal and fetal lipid metabolism under normal and gestational diabetic conditions. Horm Mol Biol Clin Investig 2016;26:109–127.
12 Gauster M, Hiden U, Blaschitz A, Frank S, Lang U, Alvino G, Cetin I, Desoye G, Wadsack C: Dysregulation of placental endothelial lipase and lipoprotein lipase in intrauterine growth-restricted pregnancies. J Clin Endocrinol Metab 2007;92:2256–2263.
13 Gauster M, Hiden U, van Poppel M, Frank S, Wadsack C, Hauguel-de Mouzon S, Desoye G: Dysregulation of placental endothelial lipase in obese women with gestational diabetes mellitus. Diabetes 2011;60:2457–2464.
14 Desoye G, Shafrir E: Placental metabolism and its regulation in health and diabetes. Mol Aspects Med 1994;15:505–682.
15 Pathmaperuma AN, Mana P, Cheung SN, Kugathas K, Josiah A, Koina ME, Broomfield A, Delghingaro-Augusto V, Ellwood DA, Dahlstrom JE, Nolan CJ: Fatty acids alter glycerolipid metabolism and induce lipid droplet formation, syncytialisation and cytokine production in human trophoblasts with minimal glucose effect or interaction. Placenta 2010;31:230–239.
16 Prieto-Sanchez MT, Ruiz-Palacios M, Blanco-Carnero JE, Pagan A, Hellmuth C, Uhl O, Peissner W, Ruiz-Alcaraz AJ, Parrilla JJ, Koletzko B, Larque E: Placental mfsd2a transporter is related to decreased DHA in cord blood of women with treated gestational diabetes. Clin Nutr 2016;pii: S0261-5614(16)00036-4.
17 Araujo JR, Correia-Branco A, Ramalho C, Keating E, Martel F: Gestational diabetes mellitus decreases placental uptake of long-chain polyunsaturated fatty acids: Involvement of long-chain acyl-CoA synthetase. J Nutr Biochem 2013;24:1741–1750.
18 Saben J, Lindsey F, Zhong Y, Thakali K, Badger TM, Andres A, Gomez-Acevedo H, Shankar K: Maternal obesity is associated with a lipotoxic placental environment. Placenta 2014;35:171–177.
19 Hirschmugl B, Desoye G, Catalano P, Klymiuk I, Scharnagl H, Payr S, Kitzinger E, Schliefsteiner C, Lang U, Wadsack C, Hauguel-de Mouzon S: Maternal obesity modulates intracellular lipid turnover in the human term placenta. Int J Obes (Lond) 2017;41:317–323.
20 Diamant YZ, Metzger BE, Freinkel N, Shafrir E: Placental lipid and glycogen content in human and experimental diabetes mellitus. Am J Obstet Gynecol 1982;144:5–11.
21 Das SK, Stadelmeyer E, Schauer S, Schwarz A, Strohmaier H, Claudel T, Zechner R, Hoefler G, Vesely PW: Micro RNA-124a regulates lipolysis via adipose triglyceride lipase and comparative gene identification 58. Int J Mol Sci 2015;16:8555–8568.
22 Visiedo F, Bugatto F, Quintero-Prado R, Cozar-Castellano I, Bartha JL, Perdomo G: Glucose and fatty acid metabolism in placental explants from pregnancies complicated with gestational diabetes mellitus. Reprod Sci 2015;22:798–801.
23 Brass E, Hanson E, O'Tierney-Ginn PF: Placental oleic acid uptake is lower in male offspring of obese women. Placenta 2013;34:503–509.
24 Sedlmeier EM, Brunner S, Much D, Pagel P, Ulbrich SE, Meyer HH, Amann-Gassner U, Hauner H, Bader BL: Human placental transcriptome shows sexually dimorphic gene expression and responsiveness to maternal dietary n-3 long-chain polyunsaturated fatty acid intervention during pregnancy. BMC Genomics 2014;15:941.