Accepted Manuscript

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PII: S0143-4004(16)30654-3

DOI: 10.1016/j.placenta.2016.12.006

Reference: YPLAC 3519

To appear in: *Placenta*

Received Date: 19 October 2016

Revised Date: 30 November 2016

Accepted Date: 5 December 2016

Please cite this article as: Gallo LA, Barrett HL, Nitert MD, Placental transport and metabolism of energy substrates in maternal obesity and diabetes, *Placenta* (2017), doi: 10.1016/j.placenta.2016.12.006.

Review: Placental transport and metabolism of energy substrates in maternal obesity and diabetes

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3,888 words

Abstract

Maternal obesity is growing in prevalence and associated with increased morbidity and mortality for both mother and child. Women who are obese during pregnancy have a greater risk of metabolic complications such as gestational diabetes mellitus (GDM) as well as type 2 diabetes after pregnancy. Children of obese and/or GDM mothers have an increased susceptibility to congenital abnormalities and a range of cardio-metabolic disorders. The placenta is at the interface of the maternal and fetal environments and, its function *per se,* plays a major role in dictating the impact of maternal health on fetal development. Here, we review the literature on how placental function is affected in pregnancies complicated by obesity, pre-gestational and gestational diabetes. The focus is on the availability of three key substrates in these conditions: glucose, lipids, and amino acids, and their impact on placental metabolic activity. Maternal obesity and diabetes are not always associated with fetal compromise and the adaptation of the placenta may partially determine the outcome. Understanding the differences in metabolic adaptation may open avenues for therapeutic development.

Key words: placenta, metabolism, obesity, diabetes, glucose, lipid, amino acids

1. Introduction

The global prevalence of overweight, obesity, and diabetes mellitus is increasing [1]. In developed nations, one third of pregnant women are overweight or obese [2] and 5-10% have diabetes in pregnancy [3]. In these complicated pregnancies, physiological changes are exaggerated, including alterations to lipoprotein levels and enhanced gluconeogenesis [4]. High maternal weight, dyslipidemia, and/or hyperglycemia place mother and child at risk, with the most common adverse outcome being high birth weight (macrosomia) [5-12]. Large for gestational age infants born to women with GDM have a higher percent body fat when compared to infants from uncomplicated pregnancies [13] and ~70% of mothers [14] and offspring [15] will develop type 2 diabetes in later life.

The influence of maternal disease on fetal outcomes is governed, to a large extent, by the placenta. In maternal obesity and hyperglycemia, placental size is greater and structural changes including thrombosis may be evident [16-19]. There are three main mechanisms that regulate fetal exposure to maternal nutrients: direct placental transfer, placental consumption, and placental conversion into alternative sources of fuel [20, 21]. While direct transfer is often regarded as the predominant pathway in regulating maternal-fetal exchange, the placenta has a high metabolic activity, which is affected by an obesogenic and/or diabetogenic environment. Alterations in placental metabolism may serve as a checkpoint to regulate fetal exposure and, ultimately, determine the degree of influence that abnormal maternal metabolism has on fetal growth and development (Figure 1) [22].

2. Glucose transport and metabolism

Glucose is the predominant source of energy for the fetus and placenta [23]. There is limited capacity for the fetus to generate its own glucose and almost all of fetal glucose is derived from the mother [24, 25]. Net glucose transfer is determined by placental transporter density, the maternal-fetal concentration gradient, and placental glucose metabolism [26].

Glucose transfer across the placenta occurs via the family of facilitated glucose transporters (GLUTs). In the human syncytiotrophoblast, GLUT1 is expressed in both

membrane fractions but there is a three- to four-fold greater expression in the microvillous versus basal membranes [27]. This ensures greater transport capacity from the maternal side and glucose transfer across the fetal side is considered a rate-limiting step. The density of GLUT1 in the basal membrane increases in the first half of pregnancy and subsequently plateaus suggesting that early pregnancy determines fetal demands for glucose transfer. GLUT1 is primarily localized to the syncytiotrophoblast but also expressed in cytotrophoblasts and fetal endothelial cells. GLUT3 is expressed in fetal arterial endothelial cells but its microvillous expression remains controversial; there are reports for its absence [28] and presence [29] at this site. The two known splice variants of GLUT9 are also expressed in placentae, with GLUT9a localized to the basal membrane and GLUT9b to the microvillous [30, 31]. GLUT4 is localized to stromal cells and not considered to contribute significantly to transplacental glucose transfer [32]. Other GLUT isoforms are either absent or expressed at very low levels in the human placenta [26]. Insulin is not considered to affect placental glucose transfer or metabolism, at least directly.

In a recent study consisting of 40 women with uncomplicated pregnancies, placental glucose transfer was quantified *in vivo* during a planned caesarean section [33]. The concentration of glucose was higher on the maternal (4.71 mmol/L) versus the fetal (3.48 mmol/L) sides, and this gradient was strongly and positively correlated with fetal glucose consumption. Maternal plasma glucose levels alone and uteroplacental glucose extraction did not correlate with fetal glucose consumption. These findings indicate that, in normal pregnancy, fetal glucose demands dictate transplacental glucose transport, rather than maternal blood glucose levels or uteroplacental glucose requirements.

In vitro experiments demonstrate that 25% of glucose that enters the placenta is metabolized, predominately into lactate via glycolysis, and the remaining 75% is delivered unchanged to the fetus [34]. However, the low metabolic rate in these experiments is explained by a low oxygen supply, which underestimates the magnitude of glucose oxidation [35]. The placenta has also been shown to synthesize glycogen [36] and, in healthy placentae explants, glucose can be incorporated into lipids [37]. Furthermore, the placenta expresses glucose-6-phosphatase suggesting capacity for gluconeogenesis [38]. The feasibility of carrying out advanced carbon tracer and imaging studies in humans is limited; however, future *in vivo* studies in other mammalian species may help to ascertain the fate of glucose once delivered to the uteroplacental unit.

105

106 *2.1 Maternal overweight and obesity*

107

108 The association between excessive maternal weight and adverse fetal outcomes,
109 including macrosomia, is well established [5] but the mechanisms describing this link have
110 not been elucidated. Birth weight, which positively correlates with maternal BMI, also
111 correlated with GLUT1 expression in isolated basal membranes [39]. However, basal
112 membrane GLUT9, and microvillous GLUT1 and GLUT9 were not increased in overweight or
113 obese women, nor was glucose transfer across either membrane.

114 Pregnancies complicated by maternal overweight or obesity are associated with a
115 proinflammatory state [40] and this has been proposed to underlie fetal macrosomia [22]. A
116 limitation of placental explant experiments is that modulatory effects of other factors, such
117 as inflammatory cytokines, growth factors, hormones, and other substrates, are often
118 ignored [39]. Visiedo *et al.* focused on the role of placental-derived hepatocyte growth
119 factor (HGF) in modulating placental metabolism in maternal obesity [19]. HGF was
120 increased in amniotic fluid and placental tissue of obese women, which increased
121 esterification, *de novo* fatty acid synthesis, and accumulation of placental triglycerides. HGF
122 also stimulated placental glucose uptake and utilization, which was facilitated by
123 augmented GLUT1 expression. Another cytokine, resistin, stimulated glucose uptake and
124 GLUT1 expression in trophoblast cells [41]. TNFα applied to syncytiotrophoblasts from lean
125 women showed reduced oxygen consumption rates in female, but not male, placentae [42].
126 However, this cannot be attributed solely to reduced glucose oxidation as the assay medium
127 contained glucose, pyruvate, and glutamine substrates. These data indicate that the
128 inflammatory profile associated with maternal overweight and obesity stimulates placental
129 glucose uptake, yet further research is necessary to describe the changes that occur to
130 placental glucose metabolism *in vivo*.

131

132 *2.2 Pre-existing diabetes and GDM*

133

134 Even in pregnancies of women with well-controlled diabetes, macrosomia remains
135 common [18, 43, 44]. In long-standing insulin-dependent diabetes, increasing birth weight
136 correlated with increasing glucose uptake and GLUT1 protein expression in basal, but not

microvillous, syncytiotrophoblast membrane vesicles [18]. Similarly, in pregnancies of pre-existing diabetes and GDM, albeit well-controlled at term, others reported upregulated GLUT1 expression (two-fold) and glucose transport (40%) in isolated syncytiotrophoblast basal membranes [45]. Once again, GLUT1 expression and glucose uptake were unaffected in microvillous membranes, which is consistent with studies in high maternal BMI [39]. Basal membrane GLUT9a is also increased in placentae from pre-existing and gestational diabetes, while microvillous membrane GLUT9b is increased only in response to exogenous insulin [31]. These data suggest that, in diabetes, the capacity for transplacental glucose transfer across the basal membrane is increased and fetal macrosomia is not merely due to increased maternal glucose. Given that basal membrane GLUT1 expression increases in early pregnancy (and plateaus thereafter), this may represent a critical period whereby transient metabolic abnormalities stimulate further increases in GLUT1 expression [18]. The expression of basal membrane GLUT1 is insensitive to glucose concentrations in the physiological range [46]. Thus, the regulation of placental glucose transporters may be multifactorial. Hyperglycemia-induced increases in fetal growth hormones, *i.e.* insulin and insulin-like growth factor-1 (IGF-1), have been regarded as potential factors as have other glycolytic intermediates and uteroplacental hypoxia. Of note, placental expression levels of GLUT3 and GLUT4 are unaltered by insulin-dependent or -independent diabetes [26].

A recent study reported that placental explants from GDM pregnancies had a two- to three-fold higher glucose uptake and a 50% reduction in fatty acid oxidation [47]. Placentae from normoglycemic pregnancies cultured in high glucose had reduced fatty acid oxidation, along with increased esterification and accumulation of triglycerides [37]. The mechanism proposed was inhibition of carnitine palmitoyltransferase (CPT1) activity by a glucose-derived by-product, malonyl-CoA. These findings were in agreement with a later study in maternal obesity, showing that heightened glucose metabolism in placental explants reduced fatty acid oxidation [19]. In women with pre-existing diabetes [48] or GDM [49], placental activity of mitochondrial electron transport chain complexes was reduced. In GDM, mitochondrial oxygen consumption was reduced, along with increased placental expression of glycolytic enzymes and LDH (marker of aerobic glycolysis) [49]. However, these women had been treated with either insulin or glyburide so effects on placental glucose metabolism cannot be definitively attributed to GDM. Collectively, these data suggest that placental glucose uptake is augmented and shunted into glycolytic pathways in

maternal hyperglycemia, and that downstream changes to fatty acid metabolism may provide a mechanistic link between maternal metabolic abnormalities and fetal fat accretion.

3. Lipid transport and metabolism

Fetal growth and development is also supported by free fatty acids and the constituent fatty acids and cholesterol that are transported in maternal lipoproteins. Markers of fetal cholesterol synthesis are very low in early pregnancy and increase only after 19 weeks gestation [50]. Placental transfer of lipoproteins is facilitated by lipoprotein receptors, lipases (lipoprotein lipase (LPL), endothelial lipase (EL), hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL)), and fatty acid binding proteins (FABPs) (Figure 2) [51-59]. Free fatty acids and lipoprotein/triglyceride fatty acids are transported into the placenta by plasma membrane FABP (FABPpm), FABP1-5, fatty acid translocase (FAT/CD36), and fatty acid transport proteins (FATP)1-4 and 6. Placental cholesterol uptake from lipoproteins occurs through scavenger receptor class B type I receptor (SRBI), low-density lipoprotein receptor (LDLR), and very low density lipoprotein receptor (VLDLR), and its efflux is mediated by ATP binding cassette transporter A1 and G1 (ABCA1 and ABCG1) [60]. Uptake of chylomicron remnant particles has also been demonstrated in the rodent placenta [61].

Maternal obesity and maternal hyperglycemia, in the setting of pre-existing diabetes and GDM, influence placental lipid transport and their frequent co-existence makes assessing the influence of each condition challenging.

3.1 Maternal overweight and obesity

Maternal obesity alters aspects of the hormonal and inflammatory milieu to which the placenta is exposed. These aspects include insulin and adipokines, such as leptin and adiponectin as well as cytokines [62, 63], and have been hypothesized to alter placental function by influencing nutrient sensing pathways including the insulin/IGF-1, mechanistic target of rapamycin (mTOR), and peroxisome proliferator-activated receptor (PPAR)-α pathways. In a mouse model of maternal obesity, activation of these pathways was observed in placental tissue [64]. Another mouse study showed that supplementation with

adiponectin (usually lower in obese women) normalized overall insulin sensitivity in the dam and placental nutrient sensing pathways [65].

Maternal high cholesterol, diabetes, and obesity influence placental expression of receptors and regulators of fatty acid and cholesterol transport. In ewes, maternal obesity was associated with increased cholesterol and triglyceride concentrations in fetal and maternal blood [66]. This was associated with elevated FATP4 protein expression as well as increased mRNA and protein expression of PPAR-γ. In a mouse model of maternal obesity, fetal liver contained 10-fold increased lipid droplets along with increased FATP6 and FABP3 protein expression in trophoblast plasma membranes [67].

In humans, maternal obesity, in concert with insulin resistance, was associated with altered placental expression of genes related to cholesterol uptake and metabolism [68]. In women with high cholesterol, placental fatty acid synthase (FAS) and sterol regulatory element-binding protein (SREBP)-2 expression were increased, with no alteration to SREBP-1 or HMG-CoA reductase (HMGR) [69]. One of the functions of cholesterol in the placenta is steroid synthesis, thus the production of placental hormones may be affected by maternal obesity. Lassance *et al.* reported obesity was associated with lower maternal plasma estradiol and progesterone levels, with reduced placental mitochondrial cholesterol and translocator protein (TSPO) expression [70].

Obesity, and the degree of maternal weight gain during pregnancy, also influences fatty acid uptake in human placenta. In women who gained weight in excess of BMI-specific guidelines, increased placental expression of system A amino acid transporter (SNAT)-1 and decreased expression of FABP3 and other genes involved in nutrient transport were evident [71]. At term, an examination of placentae from six obese women revealed increased CD36 mRNA and protein expression, decreased FATP4 and FABP1 mRNA and protein expression and FABP3 protein expression, and increased LPL activity, with no change in PPAR-α, PPAR-δ, or PPAR-γ mRNA or protein expression [56]. The authors also described decreased microvillous cytotrophoblast transport of radiolabeled linoleic acid in cells isolated from placentae of the obese women. The effect of maternal obesity on placental transfer of fatty acids may be dependent on infant gender, with oleic acid uptake in term placentae reduced in males and increased in females, and a similar trend was evident for arachidonic and docosahexanoic acid [72]. The same study also described a gender-dependent, but not BMI-dependent, effect on CD36 and FABP5 gene expression.

3.2 Pre-existing diabetes and GDM

Similar to obesity, pre-existing diabetes and GDM are associated with an altered maternal environment, including changes in circulating adipokines, growth hormones, and insulin, which can influence placental development and function. A study of 40 women showed that the insulin secretory response to an IV glucose tolerance test was positively associated with placental volume in early pregnancy [73]. In women with GDM, insulin and leptin levels are elevated, and there is activation of their receptors in the placenta [74]. Treatment with insulin in women with pre-existing diabetes and GDM positively correlates with placental expression of vascular endothelial (VE)-cadherin and β-catenin in fetoplacental vessels [75], supporting the notion that maternal insulin affects placental function directly.

Both pre-existing diabetes and GDM affect placental lipid processing but studies have primarily examined maternal type 1, rather than type 2, diabetes mellitus. To the best of our knowledge, only one study has assessed lipid processing in placentae of women with type 2 diabetes and reported decreased protein expression of PPAR-α and PPAR-γ, unchanged PPAR-δ, with increased placental lipids, nitric oxide, and peroxide content [76]. Using primary placental cell cultures, a characterization of genes involved in metabolism showed that lipid, rather than glucose, pathways were commonly activated in women with GDM [55]. Lipid modifications were not as common in placentae from women with type 1 diabetes and there was preferential activation of glycosylation and acylation pathways. In term placentae from normal weight or overweight/obese women with GDM, there were variable effects on lipid pathways depending on BMI category, including alterations in the expression of SRBI, LDLR, VLDLR, ABCA1, ABCG1, and proprotein convertase subtilisin/kexin type 9 [77].

Placental lipase expression in women with pre-existing diabetes, GDM, and obesity also show variable results, possibly due to differences in metabolic control [53], or the degree of maternal adiposity [57], triglycerides, or free fatty acids [78, 79]. Placental LPL DNA methylation is lower in GDM and negatively correlated with glucose and HDL cholesterol levels [80]. Phospholipid transfer protein (PLTP) mRNA expression is increased and not influenced by BMI in women with GDM [81]. Insulin treatment of endothelial cells

isolated from placental vessels increased PLTP levels and activity [81]. Several of the FABPs, specifically -1, -4, and -5, were reported to be increased in placentae from women with pre-existing type 1 diabetes or GDM [54, 55]. In pregnancies complicated by diabetes, raised NEFA levels may contribute to fetal macrosomia [82]. It is thought that placental transfer of maternal NEFA is increased, transported into fetal adipocytes, and esterified into triglycerides. Trophoblasts isolated from the placentae of women with GDM show reduced uptake of long chain polyunsaturated fatty acids [83] and two-fold greater triglyceride esterification in placental explants [47]. Placentae from women with type 1 diabetes showed increased placental triglyceride content [53], and increased LPL activity where infants were macrosomic [54] and decreased LPL expression where infants were of healthy weight [55]. In maternal type 1 diabetes, endothelial lipase expression in placenta was increased [53].

Placental NEFA esterification into triglycerides is thought to be increased in pregnancies complicated by hyperglycemia and/or obesity as a regulatory step to limit fatty acid transfer to the fetus [37]. However, there is no direct evidence to support this notion and earlier studies indicate that *de novo* fatty acid synthesis is not a significant contributor to triglyceride accumulation in diabetic placentae [84]. In fact, the accumulation of placental triglycerides may contribute to the proinflammatory state of complicated pregnancies. GDM has been associated with increased levels of inflammatory cytokines (IL-1β and TNFα) correlating with the induction of FAS expression [69].

4. Amino acid transport and metabolism

Amino acids are important substrates for the formation of proteins and nucleic acids in the fetus and placental transport is a tightly regulated process. Maternal amino acids are transported against the concentration gradient with placental intervillous concentrations generally exceeding maternal concentrations by two-fold [85, 86]. The concentrations in the umbilical vein mirror those of the placental intervillous space for most amino acids [85]. The high amino acid concentrations in the placental intervillous blood likely reflect active transport of amino acids from the maternal circulation to the intervillous space by syncytiotrophoblasts [85].

Amino acid transport in the placenta is facilitated by carrier proteins that are expressed on the syncytiotrophoblast microvillous and basement membranes [87]. There are 15 amino acid transport systems expressed in the placenta, seven of which are dedicated to transport of neutral amino acids (Table 1) [88]. The seven different systems for neutral amino acid transport vary in their substrate specificity and sodium dependency. Some amino acids are selectively transported by a single system whereas others can be transported by multiple transport systems.

Most amino acids are transported between the maternal and fetal circulation in both directions. Some amino acids (aspartate and glutamate) have no net transport in either direction [86], with the placenta accumulating these acidic amino acids. Glutamate is transported from fetal liver to the placenta where it is converted to glutamine, released back to the fetus, and serves as a source of energy and substrate for protein and nucleic acid synthesis [89]. The majority of studies into placental amino acid transport have clearly defined the relationship to fetal growth restriction. In obesity and diabetes, studies have primarily focused on neutral amino acid transport through systems A and L.

4.1 Maternal overweight and obesity

In obesity, altered placental neutral amino acid transport via system A contributes to macrosomia and large for gestational age infants [90, 91]. Placental gene and protein expression of SNAT1, and protein expression and activity of SNAT2 are increased [90, 92] but SNAT4 activity is decreased [91]. Increased SNAT2 activity is associated with higher circulating levels of the inflammatory cytokines, IL-6 and TNFα. These isoform-specific changes indicate that it is difficult to determine the overall effects of obesity on amino acid transport. Furthermore, relatively small sample sizes and varying degrees of obesity may contribute to the divergent results. Gender may further contribute to the disparity, with male, but not female, offspring showing positive correlations between placental SNAT1 gene expression and excess gestational weight gain [93]. Dietary fat intake alters placental system A amino acid transport in mice, which may also occur in human placenta [94]. However, the protein expression and activity of the system L amino acid transporter (LAT) is not different in obese women, not affected by gestational weight gain, nor correlated to infant birth weight [95]. Maternal plasma taurine levels are higher in obese women than in

normal-weight women with similar concentrations in the fetal circulation [96]. This is likely due to significantly decreased activity, but not amount, of the placental microvillous B transporter system in obesity and is independent of leptin and IL-6 [97].

The results indicate that obesity alters placental amino acid transport and may contribute to the fetal overgrowth commonly associated with high maternal BMI. This could be mediated by increased cytokine levels or altered levels of metabolic hormones including leptin, adiponectin, insulin, and IGF-1 and may involve signalling through insulin, mTOR, and STAT3 pathways to increase the expression of placental amino acid transporters (Figure 3) [90, 98, 99]. The effects of other hormones that are altered by maternal obesity such as fibroblast growth factor 21 (FGF21), adipocyte fatty acid-binding protein (AFABP), resistin, progranulin, and apelin on placental amino acid transport have not yet been investigated.

4.2 Pre-existing diabetes and GDM

In type 1 diabetes, amino acid concentrations in maternal plasma have been compared to weight-matched, normoglycemic plasma, with differences becoming more pronounced as pregnancy progresses [100]. In early pregnancy, only valine, lysine, and citrulline were increased and in mid-gestation, serine, lysine, proline, and arginine levels were higher but taurine levels were lower. In late gestation, amino acid plasma concentrations are higher overall with significantly higher serine, threonine, lysine, histidine, proline, and arginine concentrations in type 1 diabetes. These differences disappear post-partum and represent specific pregnancy-induced changes to amino acid metabolism. Since these women with type 1 diabetes were lean, increased birth weight may be partially explained by the increased circulating amino acids. Indeed, serine in particular, but not glucose, significantly correlated with birth weight in type 1 diabetes.

In women with type 1 diabetes, placental expression of system A neutral amino acid transporters has been reported as both increased [87] and reduced [101]. These differences may be due to small sample sizes and between-study differences in the demographic and clinical characteristics of the participants. However, since the supply of amino acids from the maternal circulation is increased in type 1 diabetes, changes to the expression and/or activity of amino acid transporters in placentae of women with type 1 diabetes may exist.

There are no reports on placental amino acid transport in the setting of type 2 diabetes. The clinical characteristics of women with type 2 diabetes resemble those of maternal obesity and/or GDM and it can be surmised that changes in placental amino acid transport are also present in women with type 2 diabetes.

In women with well-controlled GDM, the maternal concentration of ornithine only was increased [102]. However, in umbilical venous blood, methionine, isoleucine, isoleucine, phenylalanine, ornithine, glutamate, proline, and alanine were increased and glutamine was decreased. In large for gestational age infants from mothers with type 1 diabetes or GDM, placental leucine transport was increased [103]. These disparities between maternal and fetal concentrations indicate that placental amino acid transport is altered in GDM. High glucose and leptin concentrations, as commonly observed in GDM, but not insulin or TNFα, inhibited placental uptake of methionine via LAT *in vitro* [104]. In GDM, placental gene expression of IL-1β and TNFα were increased [105], which could result in higher expression of SNAT2, similar to what is observed in obesity. Since obesity is a risk factor for the development of GDM, the effects of pro-inflammatory cytokines and hormones including insulin, adiponectin, and leptin on amino acid transport in the placenta could be further compounded.

5. Conclusions

In pregnancies complicated by obesity and/or diabetes, glucose appears to be the preferred energy substrate for placental metabolism, its uptake increasing in both states. Glucose transport and metabolism, however, are not merely modulated by maternal glucose *per se*, but likely to involve a complex and dynamic interplay with fetal growth factors and other energy substrates. Lipid processing and transfer by the placenta is influenced in complex ways by maternal BMI, glucose status, and inflammation. Amino acid transport is also affected by inflammation and increased in obesity and/or diabetes in pregnancy. Whilst an increase in maternal lipids appears to be the predominant substrate in driving fetal macrosomia in maternal overweight, obesity, and/or diabetes, the combined increase in all fuels likely contributes to the increased risk of adverse fetal outcomes.

Conflict of interest

None.

Acknowledgments

LAG was supported by a fellowship from the National Health and Medical Research Council (NHMRC) and Heart Foundation (Australia). HLB is supported by an Australian Diabetes Society – Skip Martin Early Career Research Fellowship. This review was generated as part of the Queensland Perinatal Consortium Inaugural Conference held on July 15th 2016 in Brisbane, Queensland Australia. The conference was supported by an Intra-Faculty Collaborative Workshop grant from the Faculty of Medicine, The University of Queensland.

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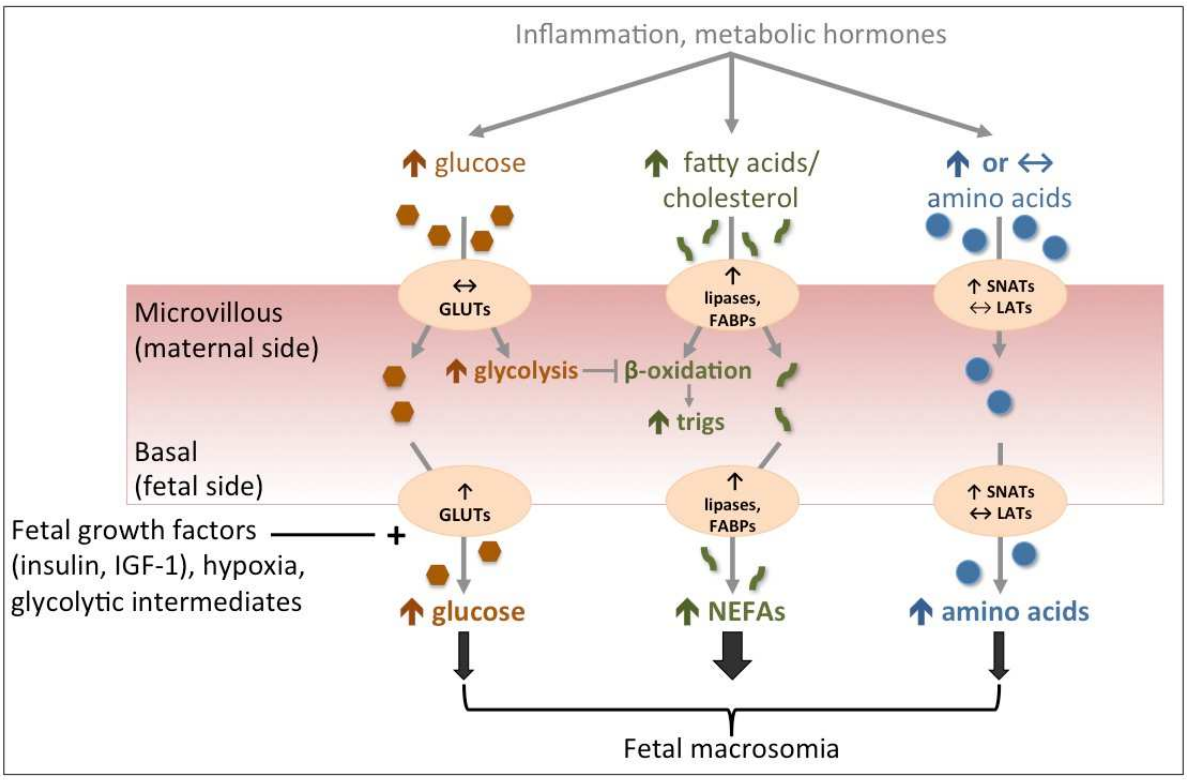
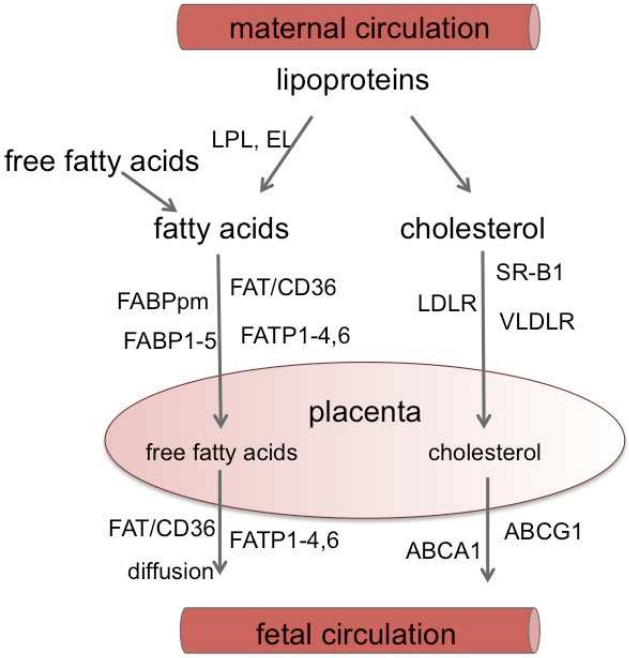
Table X Amino acid transporters in the placenta

Name	Amino acids preference for transport
Neutral amino acid transporters	
System A	alanine, serine, glutamine
System B	taurine, β-alanine
System L	leucine, phenylalanine
System N	glutamine, asparagine, histidine
System T	tyrosine
System ASC	cysteine, alanine, serine
System Gly	glycine, sarcosine
Cationic amino acid transporters	
System y^+	arginine, lysine
System $b^{0,+}$	arginine, lysine
System y^+L	arginine, lysine
Anionic amino acid transporters	
System X^-_{AG}	aspartate, glutamate





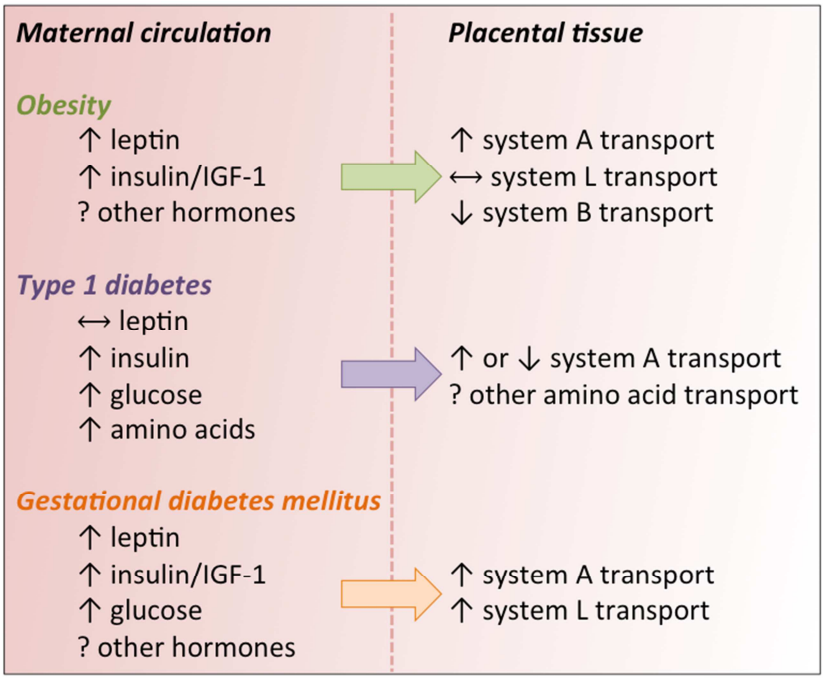


Figure legends

Figure 1 Placental transfer and metabolism of energy substrates in maternal overweight, obesity, and/or diabetes mellitus. Maternal circulating levels of glucose, fatty acids/cholesterol, and amino acids may be altered. *Glucose:* The expression of GLUTs remains unaffected in the microvillous membrane but is upregulated in the basal membrane, facilitating enhanced glucose transport across the placental-fetal side. Placental metabolism of glucose (glycolysis) is also enhanced. *Fatty acids/cholesterol:* The expression of some lipases and FABPs are increased allowing for enhanced maternal-fetal transfer of NEFAs and/or cholesterol across microvillous and basal membranes. Byproducts of glycolysis are thought to inhibit fatty acid oxidation (β-oxidation) shifting placental fatty acid metabolism to NEFA esterification and triglyceride accumulation. *Amino acids:* Maternal amino acid levels are increased in type 1 diabetes and transport via SNAT is increased. In obesity and GDM, amino acid levels are not altered but SNAT expression and activity are higher. Collectively, these modifications to substrate transport and metabolism across the placenta contribute to adverse fetal outcomes, the most common being macrosomia (weighting of block arrows signifies the magnitude of contribution). *FABPs, fatty acid binding proteins; GLUTs, facilitated glucose transporters; IGF-1, insulin-like growth factor-1; LATs, system L amino acid transporters; SNATs, system A amino acid transporters; trig, triglycerides.*

Figure 2. Putative transport of lipids across the placenta.
Fatty acids, either free or derived from lipoproteins by lipases including lipoprotein lipase (LPL) and endothelial lipase (EL) are transported into the placenta by multiple fatty acid transporters: plasma membrane fatty acid binding protein (FABPpm), fatty acid binding protein 1-5 (FABP1-5), fatty acid translocase (FAT)/CD36 and fatty acid transport protein 1-4 and 6 (FATP1-4,6). The fatty acids are then either metabolized in the placenta for energy use or storage in lipid droplets or transported to the fetal circulation by passive diffusion or carried by FAT/CD36 or FATP1-4,6. The cholesterol moiety of lipoproteins can be taken up by the cholesterol receptors for LDL cholesterol (LDLR), for VLDR cholesterol (VLDLR) or for HDL cholesterol (scavenging receptor class B type 1, SR-B1). Cholesterol is then metabolized in the placenta or effluxed to the fetal circulation as a lipoprotein by the ATP binding cassette transporters A1 (ABCA1) and ABCG1).

Figure 3. Circulating metabolic factors and placental amino acid transporters in obesity, type 1 diabetes, and gestational diabetes mellitus. In maternal obesity, metabolic hormones are generally elevated and there is increased expression of system A, unchanged expression of system L, and decreased expression of system B amino acid transporters in placental tissue. In maternal type 1 diabetes, metabolic hormones, with the exception of leptin, are elevated as are circulating concentrations of some amino acids. There are reports of increased and decreased system A amino acid transport in the placenta and effects on other amino acid transport pathways are unknown in type 1 diabetes. In gestational diabetes mellitus, metabolic hormones are typically elevated in the maternal circulation and placental system A and L transport are increased. There are no reports on placental amino acid transport in the setting of type 2 diabetes. *IGF-1, insulin-like growth factor-1.*