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REVIEW

Placental transport in response to altered maternal nutrition

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The mechanisms linking maternal nutrition to fetal growth and programming of adult disease remain to be fully established. We review data on changes in placental transport in response to altered maternal nutrition, including compromized utero-placental blood flow. In human intrauterine growth restriction and in most animal models involving maternal undernutrition or restricted placental blood flow, the activity of placental transporters, in particular for amino acids, is decreased in late pregnancy. The effect of maternal overnutrition on placental transport remains largely unexplored. However, some, but not all, studies in women with diabetes giving birth to large babies indicate an upregulation of placental transporters for amino acids, glucose and fatty acids. These data support the concept that the placenta responds to maternal nutritional cues by altering placental function to match fetal growth to the ability of the maternal supply line to allocate resources to the fetus. On the other hand, some findings in humans and mice suggest that placental transporters are regulated in response to fetal demand signals. These observations are consistent with the idea that fetal signals regulate placental function to compensate for changes in nutrient availability. We propose that the placenta integrates maternal and fetal nutritional cues with information from intrinsic nutrient sensors. Together, these signals regulate placental growth and nutrient transport to balance fetal demand with the ability of the mother to support pregnancy. Thus, the placenta plays a critical role in modulating maternal–fetal resource allocation, thereby affecting fetal growth and the long-term health of the offspring.

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Introduction

Maternal nutrition has a profound impact on fetal development and growth and influences the future health of the offspring.[1,2] However, the mechanisms linking altered maternal nutrition to changes in fetal growth and developmental programming are poorly understood. Previous studies in rodents and sheep implicate changes in placental growth, structure and function as critical mediators of adverse pregnancy outcomes when maternal nutrient availability is altered.[3–9] Here, we review changes in placental nutrient transport in response to altered maternal nutrition in pregnant women and in relevant animal models. The concept of maternal nutrition is defined broadly as the ability of the maternal supply line to provide nutrients and oxygen to the placenta. Our discussion will therefore also include placental responses to compromized utero-placental blood flow, maternal hypoxia and iron deficiency.

The placental barrier and factors influencing placental transfer

Fetal nutrient and oxygen availability depend on the rate of transfer across the 'placental barrier'. In the human term placenta, there are only two cell layers separating fetal and maternal circulations; the fetal capillary endothelium and the syncytiotrophoblast (Fig. 1).[10] The syncytiotrophoblast is the transporting epithelium of the human placenta and has two polarized plasma membranes: the microvillous plasma membrane (MVM) directed toward maternal blood in the intervillous space and the basal plasma membrane (BPM) facing the fetal capillary. In the mouse and rat placenta, three trophoblast layers form the placental barrier, and accumulating evidence suggests that the maternal-facing plasma membrane of trophoblast layer II of the mouse placenta is functionally analogous to the MVM in the human placenta.[11] In the hemochorial placenta of primates and rodents, the trophoblast is directly in contact with maternal blood. However, in the synepitheliochorial placenta of the sheep the maternal capillary endothelium and uterine epithelium remain intact and fetal binucleate cells migrate and fuse with the uterine epithelium, creating a syncytium of mixed maternal and fetal origin.[12,13]

Net maternal–fetal transfer is influenced by a multitude of factors. These include utero-placental and umbilical blood flows, available exchange area, barrier thickness, placental metabolism, concentration gradients and transporter expression/activity in the placental barrier. Placental transfer of highly permeable molecules such as oxygen is non-mediated and particularly influenced by changes in barrier thickness, concentration gradients, placental metabolism and blood flow.[14] In contrast, the rate-limiting step for maternal–fetal transfer of many ions

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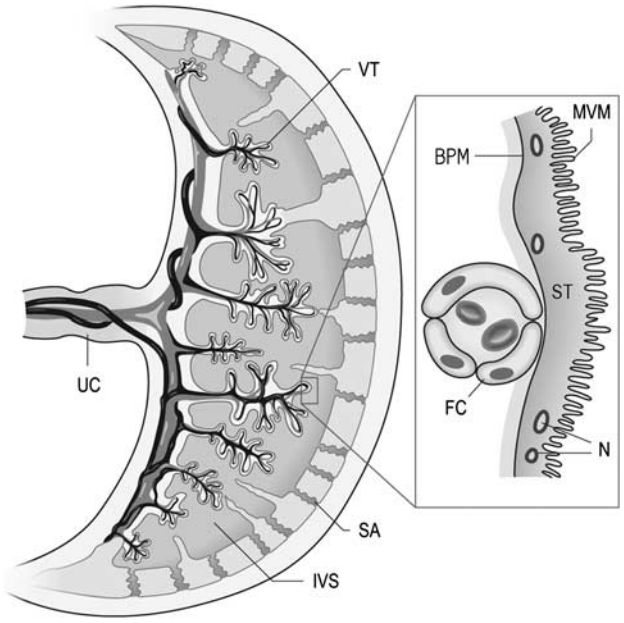

Fig. 1. The placental barrier in the human term placenta. The figure represents a cross-section of the human placenta. The insert to the right shows a schematic illustration of the placental barrier, which at term mainly consists of the syncytiotrophoblast (ST) cell and the fetal capillary (FC) endothelial cell. Of these structures, it is primarily the two polarized syncytiotrophoblast plasma membranes, the microvillous plasma membrane (MVM) and the basal plasma membrane (BPM) that restrict the transfer of molecules like ions and amino acids. N, nucleus of syncytiotrophoblast cell; IVS, intervillous space; SA, spiral artery; VT, villous tree; UC, umbilical cord. Reproduced by permission from Elsevier Ltd.

and nutrients, such as amino acids, is the transport across the two plasma membranes of the syncytiotrophoblast, which express a large number of transporter proteins. Thus, changes in expression or activity of placental nutrient and ion transporters in response to altered maternal nutrition may influence fetal nutrient availability and growth. Regulation of placental nutrient transporters may therefore constitute a link between maternal nutrition and developmental programming.

In this review, we will focus on changes in transporter activity determined *in vitro* and transplacental transport measured *in vivo*. Furthermore, we will discuss factors circulating in maternal and fetal blood and placental signaling pathways that have been shown to regulate key placental nutrient transporters. A detailed discussion of general mechanisms of maternal–fetal exchange, placental blood flow, metabolism, energy availability and ion gradients, all factors affecting placental transport indirectly, is beyond the scope of this paper and have been reviewed elsewhere.[15–18]

Placental transport in response to maternal undernutrition: two models

There are two fundamentally different, but not mutually exclusive, models for how the placenta responds to changes in maternal nutrition (Fig. 2). In the *placental nutrient sensing model*,[3,8,19] the placenta responds to maternal nutritional cues, resulting in downregulation of placental nutrient transporters in response to maternal undernutrition or restricted utero-placental blood flow. As a result, fetal nutrient availability is decreased and intrauterine growth restriction (IUGR) develops (Fig. 2). Placental nutrient sensing therefore represents a mechanism by which fetal growth is matched to the ability of the maternal supply line to allocate resources to the fetus. In this model, changes in placental growth and nutrient transport directly contribute to or cause altered fetal growth. On the other hand, predominantly based on elegant mouse studies it has been proposed that placental function is primarily controlled by fetal demand.[20–22] In response to maternal undernutrition or restricted utero-placental blood flow, resulting in decreased placental transfer and limited fetal nutrient availability, the *fetal demand model* predicts that the fetus signals to the placenta to upregulate placental growth and nutrient transport (Fig. 2). This model represents a classical homeostatic mechanism by which the fetus compensates for changes in nutrient availability by regulating nutrient supply (i.e. placental transport) in the opposite direction.

In the subsequent sections, we will discuss the evidence for these two models and explore maternal and fetal nutritional cues that may be important regulating placental growth and nutrient transport. Subsequently, we will present a model in which fetal demand and placental nutrient sensing are integrated.

Decreased maternal nutrient availability

There is a wealth of information on the impact of impaired placental blood flow on placental transport functions in humans. However, no studies are available exploring the effects of maternal undernutrition on placental transport in pregnant women. In contrast, the placental response to maternal nutrient restriction has been investigated in some detail in animal models.

Studies in humans

In general, maternal undernutrition throughout pregnancy inhibits placental growth as shown by detailed studies of pregnancy outcomes during and after the Dutch famine 1944–1945.[23] However, maternal undernutrition restricted to first trimester resulted in increased placental weight at term.[23] The effects of maternal dietary restriction on placental transport in pregnant women are unknown. In contrast, there is an abundance of data, predominantly obtained *in vitro*, describing changes in placental transport capacity in pregnancies complicated by IUGR (Table 1).[19,24–26]

In most of these studies, IUGR was caused by 'placental insufficiency', suggesting that the primary defect might have been a failure in the normal increase of utero-placental blood flow with advancing gestation. A subgroup of IUGR fetuses are

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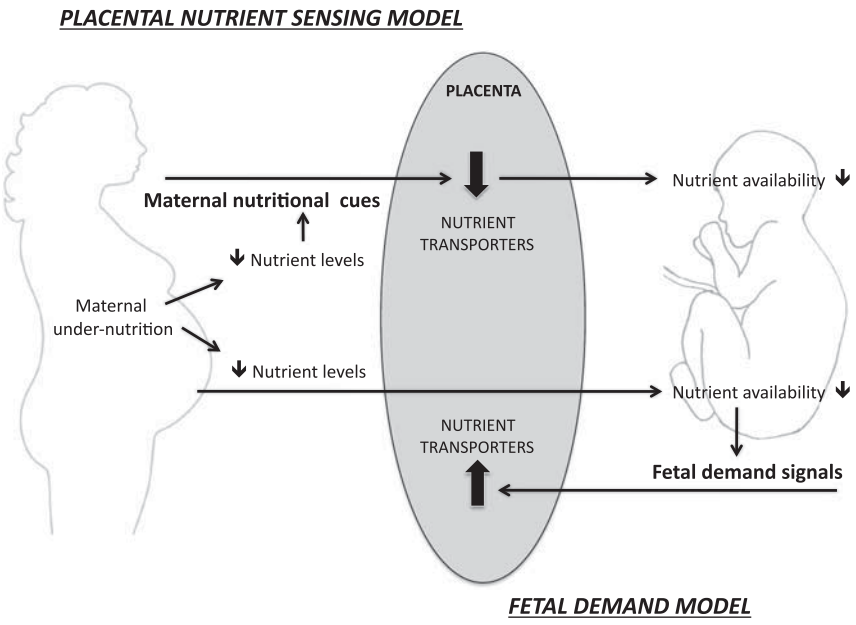

Fig. 2. Placental nutrient transport in response to maternal undernutrition: two models. Schematic representation of the two models proposed for the regulation of placental function in response to maternal undernutrition (see text for details). The *fetal demand model* (bottom) predicts that the fetus signals to the placenta to upregulate placental growth and nutrient transport to meet fetal nutritional demands. In the *placental nutrient sensing model* (top), the placenta responds to maternal nutritional cues, resulting in downregulation of placental nutrient transporters, which leads to decreased fetal nutrient availability and intrauterine growth restriction.

Table 1. *Placental transport in human IUGR*

Transport system	MVM	BPM	References
System A	↓	↔	27–30
System L	↓	↓	31
System β	↓	↔	32,33
Lysine	↔	↓	31,34
Glucose	↔	↔	28,35
Lipoprotein lipase	↓	nd	36
Ca^{2+} ATPase	nd	↑	37
Na^{+}/H^{+} exchanger	↓	nd	29,38
Lactate	↔	↓	39
Na^{+}/K^{+} ATPase	↓	↔	40

IUGR, intrauterine growth restriction; MVM, microvillous plasma membrane; BPM, basal plasma membranes; nd, not determined.

Increased (↑), unaltered (↔) or reduced (↓) transporter activity in MVM and BPM isolated from human pregnancies complicated by IUGR at term as compared with appropriate-for-gestational age controls.

hypoglycemic *in utero*,[41] however, this appears not to be due to a decreased transport capacity for glucose across the placental barrier.[28,35] In contrast, restricted fetal growth due to maternal hypoxemia at high altitude may be associated with decreased placental glucose transport capacity, as indicated by downregulation of glucose transporter (GLUT) expression in BPM.[42]

System A is a Na^{+}-dependent transporter mediating the cellular uptake of non-essential neutral amino acids.[43] System A activity establishes the high intracellular concentration of amino acids like glycine, which is used to exchange for extracellular essential amino acids via System L. Thus, System A activity is critical for placental transport of both non-essential and essential amino acids. System A activity has consistently been reported to be decreased in the MVM, the rate-limiting step in transplacental amino acid transfer, isolated from IUGR placentas.[27–30] Furthermore, the most severe cases of IUGR, as defined by abnormal pulsatility index in the umbilical artery and abnormal fetal heart rate tracings, are associated with the most pronounced decreases in MVM System A activity.[29] In contrast to these findings in 'idiopathic' IUGR, Shibata *et al.*[44] reported that placental System A activity, as measured in villous explants, was not altered in placentas of small-for-gestational age (SGA) babies in pregnancies complicated by preeclampsia.

The mechanisms underlying these interesting differences between IUGR/SGA pregnancies with and without preeclampsia remain to be established. However, the difference may be related to the observation that preeclampsia is characterized by increased maternal levels of hormones, including insulin and leptin, which are well established to stimulate placental System A activity *in vitro*.[45,46] A recent report demonstrated that homocysteine is a competitive inhibitor of System A transport.[47] Thus, despite the unchanged *in vitro* System A activity in placentas of SGA babies from pregnancies complicated by preeclampsia,[44] it is possible that increased

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circulating maternal levels of homocysteine observed in this syndrome may decrease placental System A activity *in vivo*.

The activities of transporters of essential amino acids, such as System β (transporting taurine) and System L (mediating the uptake of a range of essential amino acids including leucine) are reduced in MVM and/or BPM isolated from IUGR placentas (Table 1). These *in vitro* findings are consistent with stable isotope studies in pregnant women demonstrating that placental transfer of the essential amino acids leucine and phenylalanine is reduced in IUGR at term.[48,49] Furthermore, a reduced placental capacity to transport amino acids is in agreement with studies showing reduced circulating amino acids, in particular essential amino acids, in IUGR fetuses.[50–52] The activity of MVM lipoprotein lipase (LPL), which mediates the first critical step in transplacental transfer of free fatty acids (FFA), is reduced in IUGR.[36] These data are in line with clinical studies showing lower fetal/maternal plasma ratios for long-chain polyunsaturated fatty acids (LCPUFAs) in IUGR.[53]

Key placental ion transporters are also affected when fetal growth is restricted. The activities of Na^+/K^+-ATPase, the Na^+/H^+ exchanger and lactate transporters are downregulated in IUGR.[29,38–40] These membrane transport systems are involved in pH regulation, vectorial Na^+ transport and maintenance of the Na^+ gradient that drives the transport of other vital nutrients such as amino acids. Some ions, however, appear to be regulated quite differently. In particular, Ca^{2+}-ATPase is upregulated in BPM isolated from IUGR placentas.[37]

In summary, these studies show a downregulation of key placental transporters for amino acids, lipids and ions in human IUGR. However, most of these studies were performed at term, or in a few cases using tissue obtained from pre-term deliveries in third trimester,[28,38] and it is possible that compensatory changes consistent with fetal demand signals may be present earlier in pregnancy. Furthermore, the distinct upregulation of BPM Ca^{2+}-ATPase activity in IUGR placentas[37] may represent a compensatory activation of the placental calcium transport system stimulated by an increased fetal demand. Despite these caveats, the available information from IUGR in humans is in general agreement with the *placental nutrient sensing model* for regulation of placental transporters.

Studies in animal models

The effect of maternal undernutrition on placental growth in animal models appears to depend on the species under study and the timing, duration, type and degree of nutrient restriction. For example, in sheep, a 50% calorie restriction during the first half of pregnancy increased placental weights at term.[54] Similarly, a 50% reduction in protein intake in rats starting 2 weeks before pregnancy and maintained throughout gestation resulted in higher placental weights close to term.[55] In contrast, 30% calorie restriction throughout pregnancy in the baboon reduced placental weights by 18% near term.[56] Similarly, 40% calorie restriction from gestational days (GDs) 25 to 65 in the guinea pig,[57] 50% reduction in calorie intake in the second half of pregnancy in the rat[58] and 75% protein restriction in the rat caused placental growth restriction.[3,4]

Studies in the non-human primate and in the rat indicate that maternal undernutrition downregulates placental nutrient transporter expression and activity. Preliminary observations show that 30% global maternal nutrient restriction from GD 30 in the baboon results in downregulation of MVM amino acid and GLUT isoforms close to term (GD 165, term = 184) and decreased circulating fetal levels of essential amino acids.[59] A number of studies in the rat, employing *in vivo* measurements of transplacental transfer of isotope-labeled substrate analogs, have shown that placental capacity to transport neutral amino acids and glucose in response to calorie or protein restriction is decreased in late pregnancy.[60–63] In contrast, Ahokas *et al.*[64] found no significant change in *in vivo* placental amino acid transport near term in rats subjected to 50% calorie restriction. However, other investigators using a similar protocol have reported downregulation of placental GLUT3[65,66] and sodium-dependent neutral amino acid transporter (SNAT)1 and 2 protein expression[65] and upregulation of placental SNAT4 protein expression.[65]

Protein restriction in pregnant rats have been shown to decrease the *in vitro* activity of specific placental amino acid transporters close to term.[4] Using the same model, we studied placental transport in the unstressed chronically catheterized animal at GDs 15, 18, 19 and 21 (term at GD 23), and reported that downregulation of the placental System A transporter activity precedes the occurrence of IUGR.[3] These findings suggest that, in this model, decreased placental amino acid transport is a cause of IUGR, rather than a consequence. Furthermore, MVM protein expression of specific System A (SNAT1 and 2) and System L (LAT1 and 2) amino acid transporter isoforms was decreased in response to a low-protein diet.[8] In contrast, maternal protein restriction did not affect placental glucose transport.[3] Notably, downregulation of placental amino acid transport was observed at GD 19, and there was no evidence of compensatory upregulation before this gestational age.[3,8] These data indicate that fetal demand signals may not be present in this model, at least not from GD 15 and onwards. Overall, these observations in the baboon and rat are consistent with the *placental nutrient sensing model* for regulation of placental transporters.

A series of studies in mice have provided evidence for compensatory upregulation of placental nutrient transporters in response to maternal undernutrition.[67–69] A 20% reduction in calorie intake from embryonic day (E)3 resulted in decreased placental but not fetal weight at E16 and reductions in both placental and fetal weights at E19. Placental gene expression of GLUT1 was decreased at E16, but increased at E19. At E19, placental gene expression of SNAT2 was found to be increased but SNAT4 gene expression was decreased.[67,68] Whereas placental transport capacity for glucose

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was maintained at E16 and E19, placental capacity to transport neutral amino acids was increased at E19.[67,68] In addition, Coan *et al.*[69] explored the effect of a moderate (−22%) and severe (−61%) reduction in protein intake on placental transport function in mice *in vivo*. Whereas placental capacity to transport glucose was increased at E16 in both protein restriction groups, at E19 it was elevated only in the group subjected to severe protein restriction. In contrast, placental amino acid transport capacity was unchanged at E16 but decreased in the moderate protein restriction group at E19. Placental gene expression of GLUT1 was increased at E16 in the moderate, but not in the severe, protein restriction group, but was unaltered at E19. At E16 placental gene expression of SNAT2 was found to be increased in the severe protein restriction group, whereas at E19, SNAT1 gene expression was decreased in the severe restriction group and SNAT4 gene expression was reduced in both protein restriction groups.[69] These studies suggest that placental nutrient transport appears to be regulated differently by maternal undernutrition in the mouse as compared with the non-human primate and the rat.

The distinct placental responses to maternal undernutrition in the mouse and the rat could reflect true species differences, but may also be related to subtle differences in the feeding paradigms. In addition, the tracer methodology used in all these studies is sensitive to differences in circulating concentrations of the endogenous substrate for the transporter under study. Thus, the marked hypoglycemia (27–58% lower glucose levels than controls) reported for mice subjected to 20% calorie restriction[67,68] or moderate/severe protein restriction,[69] as well as a 32% reduction in maternal α-amino nitrogen in response to calorie restriction,[67] could result in significant overestimation of transplacental transport of glucose and amino acids. Collectively, these studies in the mouse are in general agreement with the model that fetal demand signals play an important role in modulating placental nutrient transport in response to changes in maternal nutrition.

Because compromized utero-placental blood flow is believed to be involved in many clinical cases of IUGR secondary to placental insufficiency,[70] fetal outcomes and developmental programming have been extensively studied in animal models of restricted utero-placental blood flow. In some of these studies, placental transport functions have been assessed. Uterine artery ligation in the rat resulted in IUGR and decreased transplacental transport of glucose and amino acids *in vivo*.[71] In contrast, neither the activity of the System A transporter measured *in vitro* in the maternal-facing plasma membrane of rat syncytiotrophoblast[72] nor the placental expression of GLUT1 and GLUT3[73] were altered in this model. In guinea pigs, we performed unilateral uterine artery ligation in mid-pregnancy (GD 35) and determined placental blood flows and transport of neutral amino acids and glucose at GDs 44, 50 and 63 (term at GD 68) in chronically catheterized non-stressed animals.[74] At GD 44, modest IUGR was observed and placental capacity to transfer glucose and amino acids was maintained, whereas IUGR was more severe and placental capacity to transport amino acids was decreased at GD 50 and 63.[74] Saintonge and Rosso[75] studied placental blood flow and placental transport in relation to normal variations in fetal and placental growth in the guinea pig. They reported that placental capacity to transport glucose and amino acids was maintained over the range of fetal weights with the important exception of the smallest fetuses in which placental capacity to transport amino acids was decreased.[75] Naturally occurring 'runts' in the guinea pig therefore have the same decrease in placental amino acid transport capacity as experimentally induced IUGR.[74] These observations are in contrast to intra-litter variations in placental nutrient transport and fetal growth in mice, where placental amino acid transport capacity and SNAT2 expression have been reported to be increased in the smallest placentas.[76]

There are numerous approaches to induce IUGR in the sheep. A model involving exposure of the ewe to high ambient temperature, which decreases utero-placental blood flow and placental growth resulting in asymmetric IUGR, resembles placental insufficiency in humans.[77] Because maternal and fetal vessels in the sheep are accessible to chronic catheterization, allowing for precise measurements of nutrient fluxes across the placenta, a body of information on placental nutrient transport in this model is available. For example, the placental capacity to transport glucose,[78] leucine,[79] threonine[80] and aminocyclopentane-1-carboxylic acid (ACP)[81] (a branched-chain amino acid analog) is reduced in this IUGR model. Taken together, studies of utero-placental insufficiency and IUGR in a range of animal models show that placental nutrient transport is downregulated. These findings are reminiscent of the human data and support the *placental nutrient sensing model*.

Effects of altered levels of micronutrients on placental transport have received little attention, with the possible exception of maternal iron deficiency, which results in maternal and fetal anemia and IUGR.[82,83] However, fetal anemia typically is less severe than maternal anemia suggesting compensatory mechanisms, possibly at the placental level. Indeed, maternal iron deficiency in the rat results in upregulation of the placental transferrin receptor, which is expressed in the trophoblast maternal-facing plasma membrane and mediates iron uptake into the placenta. Furthermore, maternal iron deficiency increases the expression of placental divalent metal transporter 1 (DMT1), which transports iron out of the lysosome into the cytoplasm of the trophoblast.[84] It is likely that iron itself represents the signal mediating these changes in placental expression because iron-responsive elements are present in both the transferrin receptor and DMT1 genes. However, whether other signals, such as local hypoxia or signals originating in the fetus, are also involved remain to be established.

Increased maternal nutrient availability

Most human and animal studies of the effect of increased maternal nutrient availability on placental transport have been focused on diabetes, whereas maternal obesity has attracted much less attention.

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Studies in humans

Diabetes in pregnancy, especially if poorly controlled, is associated with intermittently elevated maternal levels of glucose, amino acids and FFA and can therefore be regarded as a condition of increased nutrient availability. Although many studies in pregnant women with diabetes indicate an increased placental capacity to transfer nutrients, data is less consistent than for decreased maternal nutrient availability. Pregnancy can be complicated by type 1, type 2 or gestational diabetes (GDM), and of these conditions GDM is the most common affecting 2–10% of all pregnancies in the United States. However, the prevalence of GDM is expected to increase by two- to three-fold if the new diagnostic criteria of the Hyperglycemia and Adverse Pregnancy Outcome study is fully adopted.[85] With the exception of subgroups of women with type-1 diabetes who develop vascular complications, diabetes in pregnancy, in particular GDM, is associated with fetal overgrowth.[85] Placental nutrient transport capacity in diabetes associated with fetal overgrowth has been studied in isolated syncytiotrophoblast plasma membranes (Table 2).

Available data on trophoblast amino acid transporter activities in pregnancies complicated by maternal diabetes are inconsistent. Dicke and Henderson[92] found no differences in the uptake of neutral amino acids into MVM isolated from GDM pregnancies as compared with controls, however, these subjects did not give birth to larger babies. System A amino acid transport activity was reduced and System L transport activity unaltered in MVM isolated from pregnancies with type-1 diabetes and fetal overgrowth.[87] In contrast, we found that the activity of MVM System A transporter was increased in type-1 diabetes, independent of fetal overgrowth, and placental transport of leucine was increased in GDM.[86] These discrepant findings may be related to differences in methodology or in study populations. Notably, although birth weights were similar in the two latter reports, placental weights were 100–300 g higher in the diabetic groups in the Swedish study.[86] This may indicate that the two study populations differ in some fundamental way with regard to, for example, ethnicity, nutrition or clinical management.

Table 2. *Placental transport in fetal overgrowth in association to maternal diabetes*

Transport system	MVM	BPM	References
System A	↑,↓	↔	86,87
System L	↑[a],↔	↔	86,87
System β	↔	↔	86
Lysine	↔	↔	86
Glucose	↔	↑[b]	88–90
Lipoprotein lipase	↑	nd	36
$Ca2^{+}$ ATPase	nd	↑	37
$Na+/K^{+}$ ATPase	↔	↔	91

MVM, microvillous plasma membrane; BPM, basal plasma membrane; nd, not determined.

Transporter activity per mg of membrane protein was measured in isolated MVM and BPM vesicles. The table shows the transport activity in cases of fetal overgrowth in relation to gestational age matched appropriately grown controls: increased (↑), unaltered (↔) or reduced (↓) transporter activity.

[a] Only gestational diabetes.

[b] Only type-1 diabetes.

BPM glucose transport activity and GLUT1 expression are increased in type-1 diabetes,[89,90] which could enhance placental glucose transport even during normoglycemia. Indeed, these changes have been proposed to contribute to fetal overgrowth in type-1 diabetes with apparent optimal glucose control.[89] Recently, it was reported that the protein expression of GLUT9 is upregulated in MVM and BPM isolated from placentas of women with diabetes,[93] adding to the evidence of increased placental glucose transport capacity in this pregnancy complication. On the other hand, using placental lobuli perfused *in vitro*, Osmond *et al.*[94] showed that placental glucose transport was decreased in GDM pregnancies with normal fetal growth; however, these changes were normalized in GDM women treated with insulin.[95] It has been suggested that GLUT abundance in the placental barrier does not affect transplacental glucose transport because glucose uptake varies with placental and umbilical blood flow.[96] Notwithstanding that changes in blood flow can alter placental glucose transport, this view may be too simplistic. BPM has much lower surface area and GLUT1 expression as compared with MVM, and it has therefore been proposed that the transfer across BPM, at least to some extent, limits the diffusion of glucose across the barrier.[35] Therefore, with all other factors kept constant, any alterations in GLUT expression/activity in the BPM is likely to alter glucose flux across the barrier.

Maternal lipoproteins are the predominant source for fetal supply of FFA. Triglyceride hydrolases in the MVM of the syncytiotrophoblast release FFA from maternal lipoproteins, allowing them to be transported across the placental barrier mediated by plasma membrane fatty acid transporters (FATP) and cytosolic fatty acid-binding proteins (FABP).[97] Although there is some controversy with respect to which type of triglyceride hydrolase constitutes the major MVM lipase activity, LPL and endothelial lipase (EL) are probably the two key hydrolases.[96,97] The activity of placental LPL has been reported to be increased in type-1 diabetes associated with fetal overgrowth.[36] Furthermore, FABP1 protein expression was upregulated in the placenta of both GDM and type-1 diabetic women giving birth to large babies.[36] Lindegaard *et al.* reported increased placental mRNA expression for EL and hormone-sensitive lipase, but not for LPL, in type-1 diabetes associated with poor metabolic control and fetal overgrowth.[98] Moreover, placental expression of FABP4[99] and EL[100] is elevated in pregnancies of obese women with GDM. These observations are consistent with an increased placental capacity to supply lipids to the fetus in

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maternal diabetes, however, considering the complexity of placental lipid transport much more work is needed to draw firm conclusions. In addition to the total amount, the FFA composition of lipids made available to the fetus is of critical importance for fetal development. Indeed, the content of LCPUFAs in plasma phospholipids has been reported to be decreased in fetuses of mothers with GDM,[101] implicating a decreased supply of these fatty acids. Altogether, the data on placental nutrient transport in pregnancies complicated by diabetes is variable. However, the capacity to transport FFA and, possibly, glucose may be increased in diabetic women, in broad agreement with the *placental nutrient sensing model.*

The effect of maternal overweight and obesity on placental function in women without diabetes remains largely unknown.[102] More than half of all US women enter pregnancy overweight or obese,[103] representing one of the most daunting problem in obstetrical practice of today. It is well established that high pre-pregnancy body mass index (BMI) is strongly associated to fetal overgrowth.[104–106] Farley *et al.*[107] reported decreased System A amino acid transport activity in placental villous fragments isolated from placentas of obese Hispanic women giving birth to normal sized babies. In contrast, preliminary studies in our laboratory show that System A activity is unaltered in MVM isolated from placentas of women with high BMI in the same population.[108] Furthermore, our preliminary data on Swedish women with varying pre-pregnancy BMI indicate that System A, but not System L, amino acid transport activity is increased in MVM isolated from placentas of obese women giving birth to large babies.[109] Dube *et al.*[110] recently reported increased placental LPL activity and gene and protein expression of CD36 in obese mothers giving birth to normal sized babies. On the other hand, placental expression of FATP4, FABP1 and 3 was decreased in placentas of obese women.[110] However, protein expression studies and LPL activity measurements in this study were done using placental homogenates, which may not represent changes in syncytiotrophoblast plasma membranes. Taken together, additional data is needed to allow firm conclusions with respect to the impact of maternal obesity on placental nutrient transport.

Studies in animal models

Reports on placental nutrient transport in animal models of diabetes lack consistency. Diabetes in pregnancy has been extensively studied in rodent models using surgical, chemical and genetic approaches to induce the disease.[111] Of these methods, administration of streptozotocin (STZ), which selectively destroys pancreatic β-cells and reduces circulating insulin resulting in hyperglycemia, has been widely employed as a model of type-1 diabetes. However, at least in earlier studies, this model was associated with severe maternal hyperglycemia raising questions with respect to its relevance to pregnant women with diabetes. Furthermore, utero-placental blood flow has been reported to be reduced in rats with STZ-induced diabetes[112,113] sometimes resulting in IUGR, complicating the interpretation of placental nutrient transport measurements in the context of increased maternal nutrient availability. Nevertheless, placental transport capacity for neutral amino acids has been shown to be decreased in STZ-treated rats.[114] Placental expression of GLUT1 is downregulated[115] or unchanged[116] in mice with STZ-induced diabetes, whereas placental GLUT3 expression is increased in this model in rats.[117] Transplacental glucose transport capacity in STZ rats *in vivo* has been reported to be decreased, unchanged or increased.[112,118,119] In addition, fatty acid transfer in STZ rats has been shown to be increased or decreased.[120–122] It is likely that the variable results on placental transport in STZ-treated rodents are related to differences in the severity of metabolic disturbance, variable effects on utero-placental blood flow and differences in methodological approaches between studies.

The impact of maternal obesity on placental transport has yet to be systematically described in well-characterized animal models. The effect of a maternal high-fat diet and/or obesity on fetal development has been explored extensively in a variety of animal models.[123,124] However, the maternal phenotype of these studies has received very little attention and it is therefore not entirely clear to which extent these models resemble obesity in pregnant women. Indeed, in many of these paradigms fetal growth is restricted, which is not the typical clinical outcome in humans.[104,105] One explanation for the development of IUGR in animal models of obesity is reduced utero-placental blood flow, which has been reported for overnourished adolescent sheep[125] and in chronically high-fat-fed non-human primates.[126] Over-nutrition of the adolescent sheep is associated with an unaltered placental glucose transport capacity.[125] In adult obese pregnant sheep provided 150% of the normal calorie intake, fetal growth was enhanced at mid-gestation but fetal weight was not different as compared with the controls close to term.[7] Interestingly, there was a marked upregulation of placental expression of FATP and increased fetal blood triglycerides in this model, in particular at mid-gestation.[7]

We explored a mouse model in which female mice were given a high-fat diet (32%) for 8 weeks and subsequently mated.[127] Dams continued their diet during pregnancy and they were studied at GD 18.5. It was demonstrated that this approach resulted in a modest increase in maternal adiposity but not obesity, a metabolic profile resembling the obese pregnant woman, without evidence of diabetes. Importantly, this paradigm resulted in a fetal overgrowth and *in vivo* transport studies demonstrated marked increases in placental clearances of both ^{3}H-methyl-glucose and ^{14}C-MeAIB in response to the high-fat diet. The increase in placental clearance rates was associated with a significant increase in GLUT1 and SNAT2 expression.[127] In a slightly different approach, Rebholz *et al.*[128] fed female mice a diet containing 16% fat diet for 4 weeks and animals were subsequently mated, which did not affect the adiposity or leptin levels of the dam but resulted in increased fetal weights close to term without affecting MVM GLUT1 expression. Collectively,

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placental transport data from animal models of obesity is still too scant to be applied to the *fetal demand* and *placental nutrient sensing models*.

Mechanisms regulating placental transport in response to changes in maternal nutrition

A detailed and full account of the mechanisms known to regulate placental transport is beyond the scope of this overview and the reader is referred to recent reviews.[18,129,130] Instead, we will briefly discuss factors reported to be altered in response to changes in maternal nutrition and also shown to regulate placental transport.

Under and overnutrition elicit changes in maternal metabolism and levels of circulating hormones, which may regulate placental function. Maternal protein restriction in the rat[3] and calorie restriction in the mouse[67] are associated with decreased maternal plasma insulin, insulin-growth factor (IGF)-I and leptin. Furthermore, Sferruzzi-Perri *et al.*[67] demonstrated that a 20% restriction in total calorie intake in mice elevated maternal corticosterone levels. Calorie restriction in non-pregnant humans and animals typically increases serum concentrations of adiponectin.[131] Maternal serum concentrations of IGF-I are decreased in human IUGR[132] and some studies indicate that maternal serum leptin concentrations are reduced in this pregnancy complication.[133] In addition, placental insulin receptor number,[134] placental insulin/IGF-I signaling activity[135] and placental leptin production[136] are reduced in IUGR. On the other hand, maternal overnutrition appears to result in the opposite hormonal changes. For example, obese pregnant women typically have higher serum levels of leptin, insulin, IGF-I and interleukin-6 and decreased serum concentrations of adiponectin as compared with pregnant women with normal pre-pregnancy BMI[137,138] and similar changes are observed in GDM.[139] Furthermore, circulating maternal leptin was found to be increased and adiponectin decreased in our pregnant mice fed a high-fat diet,[127] consistent with obese pregnant women.[138] Thus, maternal undernutrition results in a catabolic hormonal profile, whereas overnutrition causes changes in maternal hormones that promote anabolism.

The significance of these changes in the levels of maternal hormones and cytokines in response to nutrition is that these factors have been shown to regulate placental nutrient transport. For example, IGF-I,[140] insulin,[45,141] leptin[45] and cytokines[142] stimulate, whereas adiponectin inhibits trophoblast amino acid transporter activity.[143] For IGF-I and adiponectin, these findings have also been confirmed *in vivo* in the rodent.[144,145] Furthermore, administration of corticosteroids to pregnant mice inhibits placental System A activity.[146] It is important to note that receptors for many polypeptide hormones on the syncytiotrophoblast cell, including receptors for insulin, IGF-I and leptin,[147–149] are predominantly expressed in the MVM, and therefore directly exposed to maternal blood. Thus, it is likely that syncytiotrophoblast nutrient transporters are mainly regulated by maternal rather than fetal hormones.

It is reasonable to assume that maternal under and overnutrition are associated with changes in placental nutrient, oxygen and energy levels, which can regulate nutrient sensors in the placenta. Signaling pathways involved in placental nutrient sensing may include the amino acid response signal transduction pathway, AMP-activated kinase, glycogen synthase-3, the hexosamine signaling pathway and mammalian target of rapamycin complex 1.[150] Of these nutrient sensors, mTORC1 signaling may be of particular importance in linking maternal nutrition to placental nutrient transport. First, placental insulin/IGF-I signaling and fetal levels of oxygen, glucose and amino acids are altered in pregnancy complications such as IUGR,[41,50,135,151] and all these factors are well-established upstream regulators of mTORC1.[152] Furthermore, mTORC1 is a positive regulator of placental amino acid transporters,[153,154] suggesting that trophoblast mTORC1 modulates amino acid transfer across the placenta. In addition, placental mTORC1 signaling activity is changed in pregnancy complications associated with altered fetal growth and in animal models in which maternal nutrient availability has been altered experimentally. For example, placental mTORC1 activity is inhibited in human IUGR[151,154] and preliminary studies indicate an activation of placental mTORC1 signaling in association with maternal obesity.[109,155] Furthermore, placental mTORC1 activity has been reported to be decreased in hyperthermia-induced IUGR in the sheep,[156] in response to a maternal low-protein diet in the rat[8] and maternal calorie restriction in the baboon.[59] Taken together, this evidence implicates mTORC1 signaling as an important placental nutrient sensor, which may constitute a critical link between maternal nutrient availability and fetal growth.

Placental signals originating from imprinted genes regulate nutrient transport in the mouse placenta.[157] Imprinted genes are predominantly expressed from one of two parental alleles and in mice more than 70 imprinted genes have been discovered. A subgroup of these genes are imprinted only in the placenta and are involved in regulation of fetal and placental growth.[157] An example of a paternally expressed/maternally repressed placental gene is *igf-2*.[5] IGF-II regulates placental growth and therefore indirectly its transport capacity. Interestingly, Sferruzzi-Perri *et al.*[67] have provided evidence to suggest that placental *igf-2* plays a role in the placental response to maternal undernutrition in mice.[67]

Significant support for *fetal demand signals* regulating placental amino acid transport comes from studies of mice with placenta-specific knockout of *igf-2*. In this model, placental growth restriction occurs in mid-gestation and there is a temporary upregulation of placental System A amino acid transporter activity. This increased nutrient transport maintains fetal growth in the normal range until late pregnancy when compensatory mechanisms fail and IUGR develops.[5,21] Based on a comparison of the placental phenotype in complete *igf-2* knockout mice and in mice with knockout of the placental-specific *igf-2* only, it has been suggested that fetal

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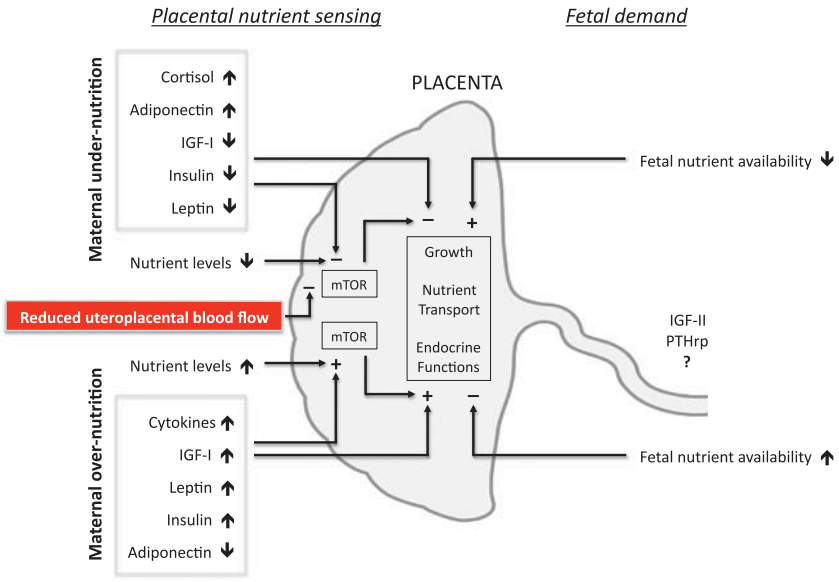

Fig. 3. Placental nutrient sensing and fetal demand: an integrated model. We propose that the placenta integrates maternal and fetal nutritional cues with information from intrinsic nutrient sensors, such as mammalian target of rapamycin (mTOR) signaling. These signals then regulate placental growth and nutrient transport to balance fetal demand with the ability of the mother to support pregnancy. Thus, the placenta plays a critical role in modulating maternal–fetal resource allocation, thereby affecting fetal growth and the long-term health of the offspring. See text for detailed explanation. IGF-II, insulin-like growth factor II; PTHrp, parathyroid hormone-related peptide.

IGF-II may be an important fetal demand signal.[158] However, at least some studies in humans have shown that IGF-II levels are reduced in IUGR fetuses[159] and higher in large-for-gestational age fetuses,[160] which is not entirely consistent with IGF-II as a fetal demand signal. In human pregnancy, it is possible that fetal parathyroid hormone-related peptide regulates the activity of the calcium pump in the syncytiotrophoblast BPM.[37,161] Additional indirect evidence for fetal regulation of placental transport functions comes from a study by Godfrey *et al.*[162] showing that MVM System A amino acid transporter activity is inversely correlated to fetal size within the normal range of birth weights. Collectively, these observations are consistent with the model proposing that placental nutrient transporters are regulated by *fetal demand*; however, the nature and identity of the fetal signals remain to be fully established.

Placental nutrient sensing and fetal demand: an integrated model

In this review, we have focused on maternal, placental and fetal signals that may regulate placental transport in response to changes in maternal nutrition, which (when defined broadly) also can include compromized utero-placental blood flow. Because placental nutrient uptake/transport is intimately related to the growth of the placenta, it is likely that the signals that regulate nutrient uptake and transport in the placenta also affect placental growth. Furthermore, by releasing an array of hormones into the maternal circulation, the placenta governs the maternal physiological adaptation to pregnancy. It is therefore plausible that changes in placental endocrine function in response to altered maternal nutrition may regulate placental growth or transport functions indirectly by affecting maternal physiology, adding an additional level of complexity. In support of this concept, emerging evidence shows that placental-specific deletion of *igf-2* increases maternal corticosterone and insulin levels and decreases plasma α-amino nitrogen.[67]

We propose a model in which the placenta integrates a multitude of maternal and fetal nutritional cues with information from intrinsic nutrient-sensing signaling pathways to balance fetal demand with the ability of the mother to support the pregnancy by regulating maternal physiology, placental growth and nutrient transport (Fig. 3). We argue that these mechanisms have evolved due to the evolutionary pressures of maternal undernutrition. Although these regulatory loops may function in the 'reverse' direction in response to overnutrition, it is possible that these responses may not be as readily apparent in maternal obesity or diabetes as in response to maternal undernutrition. Fetal demand signals are predicted to compensate for reduced nutrient availability by upregulation of placental nutrient capacity, which represents a homeostatic regulatory mechanism that is a sound strategy from an evolutionary perspective. However, the existence of maternal signals that in response to undernutrition will inhibit placental growth and nutrient transport (placental nutrient sensing) is equally important from an evolutionary point of view. Matching fetal growth to maternal resources in response to maternal undernutrition will

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produce an offspring that is smaller in size but who, in most instances, will survive and be able to reproduce. This reduced fetal growth is sometimes a better alternative than the fetus extracting all the nutrients needed for normal growth from an already deprived mother, thereby potentially jeopardizing both maternal and fetal survival. We speculate that the relative importance of placental nutrient sensing and fetal demand signals for the regulation of placental function may differ between species and depend on the type, duration and severity of the nutritional perturbation. For example, it is plausible that regulation by fetal demand signals dominates when the nutritional challenge is moderate and brief, whereas regulation by placental nutrient sensing may override fetal demand if the nutritional challenge is severe and prolonged.

Conclusion and future perspectives

Our long-term health is critically dependent on the availability of nutrients during fetal life, which is determined by placental transport. The understanding of the role of the placenta in fetal nutrition has evolved from the view that the placenta constitutes a selective but passive filter to the recognition that the placenta adapts to changes in maternal nutrition by responding to maternal nutritional cues, fetal demand signals and intrinsic nutrient-sensing signaling pathways. The complexity of these regulatory pathways is only beginning to be appreciated. A better understanding of the molecular mechanisms regulating placental transport functions may help to identify critical links between maternal nutrition, fetal growth and developmental programming. In addition, this knowledge is essential when designing novel intervention strategies. However, currently our understanding of these processes is limited, at best, presenting great challenges and opportunities for the future. For example, there is a lack of information on the (1) molecular identity of fetal demand signals, (2) the mechanisms by which lipids are transported across the placenta and the role of placental lipid transport in programming of obesity and diabetes, (3) how multiple placental nutrient-sensing signaling pathways are integrated and (4) how signals between the placenta and the mother influence maternal–fetal resource allocation. Furthermore, additional animal models that are relevant for the human condition are needed, in particular for GDM and maternal obesity. Finally, attention on the influence of fetal sex, ethnicity, maternal age and parity on placental function is required in future studies.

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