# Introduction

## Associations between maternal obesity and offspring obesity and metabolic disease

There is a significant increase in adult and childhood obesity in the United States with a

prevalence of over 39.8% and 18.5%, respectively (Hales *et al.*, 2015; Flegal *et al.*, 2016). Of concern, pre-pregnancy obesity has been increasing in tandem (Branum *et al.*, 2014). Maternal obesity has a long-term effect on the health of the mother (Sebire *et al.*, 2001) and the offspring (O’Reilly & Reynolds, 2013). Offspring of obese mothers are at a higher risk of developing insulin resistance (Samuelsson *et al.*, 2008; Mingrone *et al.*, 2008), which increases their risk of developing diabetes (Catalano *et al.*, 2009). Fetuses of obese mothers have a significantly higher HOMA-IR index compared to fetuses of lean mothers indicating that offspring insulin resistance can develop during gestation (Catalano *et al.*, 2009).

The underlying mechanisms by which maternal obesity influences offspring insulin resistance remain unclear. The placenta is the rate-limiting step for fetal nutrient acquisition, and hence, fully understanding the placental nutrient transport will help develop future treatments that limit the effects of maternal obesity on the offspring. We propose to review the hypothesis that maternal obesity influences the offspring health through altering the maternofetal interface and placental transport capacity. The placenta is highly regulated to ensure adequate growth of the fetus in normal pregnancies (Gude *et al.*, 2004), but in obesity, placental transport capacity is modified. We will focus on the role of the placenta in modulating altered offspring outcomes, recent findings on placental micro- and macronutrient transport, and the underlying mechanisms and metabolic pathways that result in the impaired placental function. This review will also help bridge the gap in knowledge between potential mechanisms that alter the placental nutrient transport and the offspring risk of disease.

Emerging evidence shows that a disruption in the placental growth or structure not only impacts the fetus, but also the mother. Considering that the placenta is an active organ that responds to endocrine, autocrine and paracrine signals, an alteration to its structure affects the mother through transmitting hormonal signals to the maternal circulation and affects the fetus by altering nutrient and oxygen supply and hormonal signals that may aid in growth. Human chorionic gonadotropin hormone, released by the syncytiotrophoblasts, serves in maintaining the corpus luteum which allows for a constant progesterone secretion till about ten weeks of gestation until the placenta is fully developed to take over the corpus luteum function.

# Defining the Placenta

## Overall structure and function of the human and non-human placenta

The placenta is the first organ that reaches full maturation during human pregnancy. The human placenta is composed of layers with various functions in the materno-fetal interface. The human placenta has two membranes, a microvillous membrane (MVM) that faces the maternal side and is in direct contact with the maternal circulation, and a basolateral membrane (BM) that is on the fetal side and is in direct contact with the fetal endothelium and capillaries where the nutrient and gas exchange to the fetus occurs through transporters. The cell types lying between the maternal and fetal blood have varying roles and maturation speed. Moving inwards from the maternal membrane to the fetal membrane, the cell types include endovascular cytotrophoblasts, extravillous cytotrophoblasts, syncytiotrophoblasts, villous cytotrophoblasts, cytotrophoblasts and fetal endothelial cells.

Non-human placenta, mainly that of mice, has different cell types but possesses the same discoid structure that the human placenta has. Due to natural differences between mammalian physiology, the placental growth and differentiation is unique to each species. There is a number of differences between the human and animal placenta that include the gestation age, litter size, maturation of the placenta, function of cell types in the placenta, transporter expressions on the placental membranes, differences in interhemal layers and histological differences. The mouse has an inverted yolk sac placenta that is active throughout gestation. The human yolk sac, although evident during the first trimester, becomes inactive after the full maturation of the placenta. Furthermore, the mouse placenta has more cell types and membranes than the human placenta. Moving inwards from the maternal membrane of the placenta to the fetal membrane, the mouse placenta has trophoblast giant cells, spongiotrophoblast cells, two syncytial trophoblast layers, mononuclear trophoblast cells, and fetal endothelial cells. As many layers may resemble the human placenta, it is notable that the mouse placenta has an additional membrane due to the two syncytiotrophoblast layers that are linked by gap junctions.

The trophoblasts take up the most space in the human and mouse placenta and besides having an endocrine function, trophoblasts are the main site of nutrient, gas and waste exchange between the mother and the fetus. The syncytiotrophoblast and the extravillous cytotrophoblasts are in direct contact with the maternal blood. It is worthy to note that the syncytiotrophoblast is the main part of exchange since it is the outermost layer in the fetal villous tree. The survival of the human placenta and the fetus heavily rely on the trophoblast ability to invade the maternal myometrial spiral arteries. Failure to invade the myometrium jeopardizes the placental ability to successfully exchange nutrients and gases thus risking an early termination of pregnancy or an unhealthy pregnancy. The ability to invade the maternal myometrium occurs during the first trimester and plays a role in determining pregnancy outcomes. After the first trimester, the syncytiotrophoblast undergoes a series of angiogenesis to allow for increased exchange of nutrients and gases coping with the increased fetal needs throughout gestation. The syncytiotrophoblast is also the outermost layer of the placenta facing the mother so its structural function makes it a barrier that protects the growing fetus. Finally, the syncytiotrophoblast has an endocrine function. The syncytiotrophoblast secretes the human chorionic gonadotropin (hCG), estrogens and progesterone, human placental lactogen, human placental growth hormone, insulin-like growth factor, and endothelial growth factor. The placental endocrine function is thought to be sex-specific and thus the placenta has a distinct endocrine function depending on the sex of the embryo. In mice, the placental survival does not depend on the deep trophoblastic invasion of the uterine wall, as the invasion is shallow reaching only the endometrium. Considering that the hCG gonadotropin is human specific, other placental endocrine functions vary between humans and mice. Mouse placenta has a unique set of lactogens that do not exist in humans. Furthermore, trophoblastic giant cells in the mouse placenta produce lactogen throughout gestation. The corpus luteum maintains the production of progesterone throughout the mouse gestational period, whereas in humans, the corpus luteum endocrine function to maintain pregnancy is overtaken by the placenta, specifically the syncytiotrophoblast. The definitive structure of the placenta in mice is determined almost halfway through gestation, whereas in humans, placental structure is determined very early in pregnancy at around three weeks of gestation.

## Placental differentiation and growth processes throughout gestation

In humans, after fertilization, the blastocyst attaches to the uterine wall. The trophoblasts begin a rapid series of proliferation to produce the syncytiotrophoblast and cytotrophoblast layers. The extravillous cytotrophoblast initiates its invasion of the maternal uterine wall invading the endometrium to allow for maternofetal interaction through spiral arteries. The spiral arteries, arising from the maternal uterine will be invaded by endovascular cytotrophoblasts that initially form plugs allowing maternal blood to leak to the placenta. The endovascular trophoblasts act as a barrier preventing direct maternal blood circulation in the intervillous space until the 12th week of gestation to protect the developing fetus from the highly oxygenated maternal blood. Endoglandular cytotrophoblasts invade uterine glands to allow for maternal blood flow prior to the widening of the spiral arteries and the bathing of trophoblasts and intervillous space in the placenta with maternal blood. The bathing of the trophoblasts in maternal blood does not occur until the second trimester and thus the trophoblastic invasion is vital during the first trimester to allow for nutrient and gas exchange. The cytotrophoblasts, located beneath the syncytiotrophoblast, push through the syncytiotrophoblast thus forcing it to expand into the endometrial space. Upon the successful expansion of the STB into the uterus, the fetal villi develop enabling the placenta to exchange nutrients, gases and wastes with the maternal circulation. This process of trophoblastic invasion occurs within the first weeks of gestation. Prior to the full maturation of the placenta, the fetus is thought to acquire nutrients through the nutrient endocytotic action of the syncytiotrophoblast. The cytotrophoblasts, that differentiate into syncytiotrophoblast tend to decrease after the first half of pregnancy. A failure in the trophoblastic invasion of the myometrium or the spiral artery remodeling can be a leading cause of preeclampsia or gestational complications.

In mice, the trophoblast proliferates and differentiates post-fertilization to give rise to polar trophoblastic cells and murine trophoblastic cells that differentiate into trophoblastic giant cells. On the eighth day of gestation, mesoderm cells from the embryo give rise to the yolk sac which allows nutrient exchange between the mother and the fetus throughout gestation. Part of the mesoderm invades the trophoblastic layer to establish a labyrinthine layer and a network of fetal blood vessels. The labyrinthine zone is located underneath the maternal decidual zone and the junctional zone that lies between the fetal and maternal sites. Those layers are clearly evident in the mouse placenta at 12.5 days of gestation. The junctional zone contains the trophoblastic giant cells, spongiotrophoblasts and trophoblastic glycogen cells that invade the decidua at day 13 of gestation. The labyrinthine zone, developing from the trophoblasts, contains the differentiated trophoblasts: the double syncytiotrophoblast layers and the cytotrophoblast in contact with maternal circulation. Maternal blood passes from the decidual zone through the spongiotrophoblasts in the junctional zone and into the labyrinth zone to surround the trophoblastic cells and allow for the nutrient, gas and waste exchange. As mentioned earlier, the placental complete structure is established late in pregnancy. Unlike the human placental structure that develops in the first three weeks of gestation and the human trophoblastic invasion of the myometrium that dictates fetal supply and occurs very early in pregnancy, the murine trophoblast invasion of the uterine wall occurs towards late gestation and is less critical in determining the survival of the fetus in the mouse due to the constant activity of the murine yolk sac.

## Placental responses to maternal endocrine and nutritional signals in lean and obese mothers

Not only does the placenta secrete hormones to the maternal circulation to increase the maternal catabolism and ensure the demands of the fetus and its survival, but it is additionally affected by maternal signals from the circulation. Some studies have shown that insulin like growth factor-1 stimulates fetal placental nutrient uptake by increasing the placenta glucose transporter, GLUT1 and the placental amino acid transport system, system A. Although insulin promotes the uptake of glucose in maternal cells, its activity in the placenta does not mediate glucose transport. In fact, maternal insulin levels only mediate downstream signaling molecules of insulin on the placental microvillous membrane. For instance, insulin activates mammalian target of rapamycin (mTOR) on the maternal side of the placenta causing its upregulation. In maternal obesity, the increased circulating maternal levels of insulin increase lipogenesis mediated by mTOR complex 1 (mTORC1) signals. This leads to fat deposition on the placental barrier. Maternal insulin does not cross the placenta to the fetus and thus any correlation between the maternal insulin levels and those of the fetus are not due to direct transport of maternal insulin to the fetus through the placenta but might be rather caused by downstream activities of maternal insulin that lead to an increased macronutrient flux to the fetus. The fetus, in turn, responds by increasing insulin secretion and hence, the fetus develops an increased circulating insulin level indirectly associated to the maternal levels. Insulin also stimulates system A activity, which may be altered in events of maternal obesity.

Another signaling mechanism is CCAAT-enhancer-binding protein (C/EBP) downstream of insulin. Syncytiotrophoblasts express C/EBP allowing cytotrophoblasts to differentiate to syncytiotrophoblasts in a normal placenta. In obese women, C/EBP is downregulated and its expression is decreased in syncytiotrophoblasts. The decreased C/EBP expression may yield a less mature placenta or a placenta with a suboptimal structure due to the decreased syncytiotrophoblast growth. By reducing the cytotrophoblast capacity to differentiate to syncytiotrophoblasts, the placenta of obese women will have less syncytiotrophoblasts compared to that of lean women. This mechanism may not only alter the placental structure, but also its function. A decreased endocrine function and exchange surface area, due to the decreased syncytiotrophoblast layer, would impair the syncytiotrophoblastic capability to produce hCG. Whether this mechanism may be protective to limit potential fetal overgrowth or if it results in suboptimal growth is not clearly identified.

In lean women, adiponectin levels are thought to reduce insulin sensitivity in the placenta. This is considered a protective mechanism in lean women who encounter hyperglycemic episodes, naturally postprandial. As adiponectin reduces the placental insulin sensitivity, it protects the fetus from the downstream upregulated insulin cascade which may lead to increased fetal nutrient flux. In obese mothers, this mechanism is absent, as obese mothers usually have hypoadiponectemia, which fails to protect the placental transport capacity in times of maternal hyperglycemia. Furthermore, leptin in lean women stimulates system A function. In obese women, who may suffer from hyperleptinemia and leptin resistance may have a reduced system A function. Maternal nutritional status affects hormonal regulations and can influence placental function. It remains unclear whether the maternal nutrition milieu is translated to the fetus, but the role of the placenta in determining the nutrient flux, mediated by hormonal signals or passive and active transport, is a definite moderator of this effect.

# Altered placental transport capacity in obesity

## Key nutrient transporters present on the placental maternal and fetal membranes

For nutrients to pass from the maternal circulation to the fetal circulation, it has to cross the placental barriers. In humans, nutrients need to pass through three membranes, the microvillous membrane of the syncytiotrophoblast, the basolateral membrane of the syncytiotrophoblast and the fetal endothelial membrane to reach the fetal circulation. The nutrient flux to the fetus depends on the circulating levels of maternal nutrients, the placental transporters and metabolic capacity, fetal requirements and proper maternal blood flow through the placenta. The localization of transporters across placental barriers has been studied for years, and yet there is inconsistent data and undiscovered mechanisms involved in the transport of certain nutrients, especially the impaired mechanisms in light of gestational complications. Data from this field support two schools of thought regarding the role of the placenta in nutrient transport. One theory suggests that the placenta allows for transport of nutrients in a manner that the fetal milieu reflects the maternal milieu and fetal growth adapts to the available maternal supplies. Hence, any deficiencies in the mother will be passed on to the fetus. On the other hand, others believe that the placenta has the capacity to regulate the flux of nutrients to the fetus by compensating for under or over nutrition as it senses both the available maternal nutrients and manages the flux so that it matches the fetal growth needs. The two theories may sound contradictory but they may also help justify why the fetal outcomes for obesity may be macrosomia or growth restriction supporting that maternal milieu may be reflected in the fetus or that the maternal milieu was overcompensated for by the placenta to yield either outcomes, respectively.

Transport of glucose occurs via passive diffusion mediated by glucose transporters. The fetus relies solely on circulating maternal glucose. In humans, there has been a few identified GLUT transporters expressed at different periods of gestation. GLUT3 is thought to be essential during the early stages of pregnancy, whereas GLUT1 seems to be expressed throughout gestation. The localization of the transporters is unique as GLUT 3 is mainly expressed at the syncytial membranes towards early pregnancy then limited to the fetal endothelial cells during the late periods of pregnancy. GLUT1 is expressed on the syncytial barriers but tends to have an increased expression on the microvillous membrane of the syncytiotrophoblast compared to the basolateral membrane towards late pregnancy. This might indicate that the glucose entering the placenta down the concentration gradient may be used by the placenta or stored, as transporters on the basolateral membrane are reduced, or this could indicate that the fetus depends less on glucose towards the late pregnancy stages. There is evidence showing that the placenta transforms part of the glucose to lactate to be used as a source of energy.

Around 20 transport systems of amino acids have been identified. The amino acid concentration is higher in the fetal compartment than in the maternal circulation and therefore amino acid uptake requires active transport. To allow for this transport, the microvillous membrane has more transporters than the basolateral membrane. In the basolateral membrane, the uptake becomes passive via system L transporters, LAT3 and LAT4, as the placenta holds the higher concentration gradient compared to the fetal concentration.

Lipid transport is maximized during the last trimester of gestation with evidence showing that the expression of lipid transporters on the placenta increases during the last three months of gestation. The exact mechanisms by which fatty acids are transported through the placenta remain unclear with evidence supporting passive diffusion and protein-mediated transport. The placenta allows metabolism, transport, and storage of the fatty acids and triglycerides. The transporters FATP and FABP play a major role in the transport of free and bound fatty acids. Furthermore, the placenta is capable of transporting and metabolizing triglycerides with the activity of placental lipoprotein lipase and endothelial lipase. The fetus relies on maternal supply of cholesterol, as the fetal capacity to biosynthesize cholesterol develops in later pregnancy.

According to a recent review, localization of fetal transporters across the syncytiotrophoblastic membranes was evaluated. ABC and SLC transporters differ on both membranes and regulate fetal nutrient supply. The transporters also control drug transfer from the maternal circulation to the fetal circulation.

Micronutrient transport is vital to ensure adequate fetal development and fetal and placental function. Choline is necessary during the fetal development to allow for the synthesis of phospholipids. Human data has shown that the transporters for choline are CTL1 and CTL2 localized at syncytial membranes and endothelial fetal membrane throughout gestation. Folate transporters have been localized to the placenta microvillous membrane and basolateral membrane. Folate receptor alpha was expressed on the microvillous membrane during the first trimester and at term. Reduced folate carrier was expressed on the basolateral membrane of the placenta, and proton-coupled folate transporter, PCFT, was expressed on the syncytial layer to allows for the transport of folate from the microvillous membrane to the basolateral membrane. Vitamin B 12, in the form of cobalamin, is transported from maternal circulation into the placenta by two primary transporters, transcobalamin and haptocorrin. Transcobalamin is responsible for the transport of the majority of cobalamin, and according to a novel finding, the expression of this transporter on the microvillous membrane seems to increase with gestational age and is expressed more in male offspring compared to female offspring. The exact mechanisms by which cobalamin is transported within the placenta to the fetus remain vague and require further studies. Selenium deficiency can cause drastic pregnancy outcomes like miscarriage. The fetus cannot produce selenium and requires constant supply from the maternal circulation to be able to produce selenoproteins. On the placenta, apolipoprotein E receptor-2 is expressed on the syncytial membranes and allows for the uptake of selenoprotein P via endocytosis. It appears that selenium is passively transported into the placenta and to the fetus. It is worthy of mentioning that selenium competes with sulphates to cross the microvillous membrane as both micronutrients share a common pathway. In mice, megalin is expressed in the yolk sac and contributes to the uptake of selenium to the fetus as well.

A recent study showed that 1,25-Dihydroxy vitamin D3 plays an important role in the placental amino acid transport through system A transport. Calcitriol upregulates the mRNA expression of neutral amino acid transporter SNAT2 on placental trophoblast cells. The underlying mechanisms are thought to be transcriptional but are not yet well understood. In previous studies, maternal vitamin D deficiency has been associated with suboptimal fetal growth. The suboptimal fetal development can be attributed to vitamin D’s role in regulating the extracellular cytotrophoblast cell invasion of the uterus which determines access to maternal circulation. Calcium in fetal circulations is regulated in a similar manner to adult circulations via fetal parathyroid hormone (PTH) secretions and the active form of vitamin D in the plasma. PTH secretions are thought to be regulated by calcium-sensing receptor, which is vital for transplacental calcium transport. Calcium-sensing receptor is localized at the extracellular cytotrophoblast layer, . It is determined that fetal calcium is higher than maternal calcium concentrations, and therefore, calcium transport is active. Transient receptor potential channels and calcium ATPase transporters are localized at both membranes of the syncytiotrophoblast, with calcium ATPase being primarily to be evident on the basolateral membrane. The rapid fetal development requires high amounts of calcium be transported to support fetal development. Besides meeting fetal calcium needs, calcium plays a role in placental maturation, cell signaling, and invasion. The exact mechanism by which calcium is transported to the fetus are not yet elucidated and can differ by mammalian species.

Iron recommendations increase during gestation to cope with the increased maternal and fetal circulation needs and to avoid anemia with the expected maternal blood loss post-delivery. Iron, metabolized into transferrin, binds to transferrin receptor-1 that is located on the placental microvillous membrane. Once transferrin is bound to its transporter, it is endocytosed into the placenta where transferrin receptor-1 dissociates from transferrin. It is then transferred to the fetus by ferroportin exporter located on the placental basolateral membrane of the syncytiotrophoblast and through the fetal endothelial cells by unknown mechanisms. It seems that maternal levels of transferrin dictate the expression of placental transferrin receptors. Low maternal iron concentrations cause an increase in the expression of microvillous membrane transferrin receptor-1 to compensate for the maternal deficiency and provide sufficient iron for the developing fetus. High maternal levels of iron also promote an increase in the transferrin receptor-1 expression, but since fetal liver iron levels dictate fetal iron needs, the excess iron is stored in the placenta. Placental iron transporters are not yet fully understood but are thought to increase with gestational age to meet fetal requirements. On the other hand, zinc deficiencies seem to be uncommon but can affect trophoblastic differentiation and reduce placental weight which implies a suboptimal placental function. Zinc is actively transported to the fetus via zinc transporter 5 and human Znt-like 1 which are expressed on the microvillous membrane of the placenta. Zinc levels are higher in the fetal circulation than in the maternal circulation. Endocytosis allows for the uptake of zinc by the placenta to be transported to the fetus but the mechanism are not fully understood. Contrary to transferrin, zinc transporters show a reduced expression in vitro when maternal levels are high post supplementation, and transporters increase in cases of maternal deficiency to allow for optimal zinc uptake and transport to the fetus. Interestingly, saturation of the transferrin receptor across the microvillous membrane due to increased transferrin levels causes the employment of zinc transporter ZIP 14 to allow for the uptake of excess transferrin to be stored in the placenta. Recent research showed that maternal exposure to cadmium can impair placental zinc transport and limit fetal growth. Fetal zinc needs are higher during early gestation periods.

## How micro- and macronutrient placental transporters are altered in obesity and how this affects nutrient flux and macronutrient accretion in the fetus

Maternal obesity is considered a risk factor for maternal and offspring health. Maternal obesity is usually associated with higher levels of glucose, triglycerides, insulin, leptin and inflammatory markers but lower adiponectin levels. Research has been inconsistent regarding placental transport in maternal obesity with conflicting data from human and non-human data. Furthermore, the majority of the data has focused on the syncytiotrophoblastic membranes without an emphasis on the fetal endothelial cellular membrane. In this review, we will focus on recent findings on altered placental transport mechanisms in maternal obesity absent of gestational diabetes.

Glucose transport in obesity (MOLLY’S PART TO BE ADDED)

Amino acid transport through the placenta has been the most inconsistent. Amino acid transport system A was shown to have increased activity especially with the expression of neutral amino acid transporters SNAT1 and SNAT2 on the microvillous membrane implying an increased amino acid flux to the fetus, while amino acid transport system L activity was not altered with maternal obesity. Sex differences may appear with male offspring having increased system A activity compared to females. The increased expression of the transporter system can contribute to the birth of macrosomic newborns due to the increased supply of amino acids. Earlier research demonstrated a decrease in term placental amino acid transporter activities in mothers with obesity. Most current data suggests an altered amino acid transport but the specific transport expressions remain inconclusive.

Fatty acid and cholesterol uptake and metabolism were inconsistently altered in maternal obesity. An original article demonstrated that the expression of fatty acid transporters was significantly reduced in obese rats. It is worthy to note that recent findings demonstrated an increased fatty acid esterification in the placenta, however, mitochondrial fatty acid oxidation was downregulated and compensated for by peroxisomal oxidation. The increased placental storage of fatty acids was thought to be a protective mechanism to prevent excess fatty acids from crossing the fetal-placental membrane. Further studies have found an increase in the expression of cluster of differentiation 36 (CD36) but a decrease in fatty acid transporters including fatty acid binding protein-4 (FABP-4) and endothelial lipase (EL). Emerging evidence shows that the fetal endothelial cells have a decreased fatty acid transporter expression which may indicate that the rate-limiting step of fatty acid transport could be at the fetal side despite the change in transporters at the syncytiotrophoblastic membrane.

Obesity is often associated with micronutrient deficiency, and thus the maternal circulating levels of micronutrients will determine placental responses. As mentioned earlier, the adaptations to maternal levels of circulating micronutrients are unique to every nutrient although exact mechanisms remain unclear for the transport of the majority of micronutrients.

## Alterations in metabolic and signaling pathways that result in altered nutrient transport at the placental level

Glucose transport in obesity (MOLLY’S PART TO BE ADDED)

The upregulated amino acid transporters may be attributed to increased metabolic pathways upstream of amino acid uptake like mTORC, insulin and insulin-like growth factor, leptin, and adiponectin. In lean mothers, adiponectin decreases amino acid uptake especially postprandial and is thought to be a protective mechanism to limit excessive uptake of amino acids to the fetus especially that insulin levels are elevated postprandial. Due to hypoadiponectenemia associated with maternal obesity, this mechanism is altered and the effect of adiponectin on the placenta is reduced. Maternal levels of insulin, adiponectin, leptin, and cytokines due to the inflammatory milieu induced by obesity have a significant role in regulating the downstream placental metabolic pathways of insulin, peroxisome proliferator-activated receptor alpha (PPARα) and mTORC. Maternal obesity is assumed to directly influence placental lipid metabolism with evidence suggesting a protective role of the placenta in limiting available fatty acids for fetal supply by esterifying and storing the lipids that cross the microvillous membrane. Alterations in the inflammatory milieu of the mother, which is usually elevated due to obesity, is also thought to affect placental function.

## Emerging evidence on the role of placenta in determining offspring risk of disease in human and animal models

Improper placentation has been linked to intrauterine growth restriction and the health risks associated with it. Overnutrition, in the event of maternal obesity for example, is currently being associated with altered placental transport of nutrients which alters fetal risk of developing disease. Fetuses who are overfed due to increased nutrient flux are at a higher risk of developing a similar metabolic profile as a person with obesity. The maternal milieu has a crucial role in determining the health and function of the placenta, which ultimately influences fetal health and development. A recent study in mice showed that adiponectin supplementation given during gestation prevents the adverse outcomes of maternal obesity on the fetus. Adiponectin supplementation restores adequate levels for adiponectin in the maternal circulation, and thus restores some of the placental normal sensitivity to adiponectin in maternal obesity. This study showed that adiponectin restores the normal insulin, mTORC and PPARα signals that were altered in maternal obesity. Adiponectin supplementation seems successful in restoring normal placental activity and might be a promising intervention that is yet to be translated to humans. This highlights the placental sensitivity to any alterations in the maternal environment and how the placenta can influence fetal outcomes. Other approaches to hamper outcomes of maternal obesity on the fetus incorporated exercise. Exercise in mice during pregnancy was suggested as a less invasive method to restore some of the normal functions of the placenta in light of maternal obesity. Maternal obesity caused a hypoxic placental setting and lipid accretion on the placenta, and exercise alleviated the hypoxic environment as seen by a reduction in hypoxia-inducible factor 1-alpha (HIF1A) and reduced lipid deposition on the placental zones. Exercise also had an indirect effect on the offspring outcome by which offspring of obese dams who exercised during gestation did not develop hyperinsulinemia or adipose tissue insulin resistance unlike offspring of obese dams who did not exercise during gestation. This emphasizes the role of the placenta in determining the fetal health outcome.

It is important to appreciate that maternal obesity effect on the fetus may be attenuated as further data emerges on the mechanisms underlying placental altered functions.

# Future directions

## Current gaps in our understanding of mechanisms of disrupted placental transport

Data from human and rodent models may overlap in certain findings but can mechanistically differ especially that the histology of the rodent and human placentas varies along with the dissimilarities in transporter expression, gestation period and multiple versus singleton pregnancies. In addition, the majority of studies focus on the transporters on the syncytial membrane, which is helpful in determining the flux of nutrients to the placenta, but since the placenta is metabolically active and not simply a passive conduit, the fate of nutrients in the placenta needs to be further studied and assessed. Furthermore, it is essential to emphasize the importance of the endothelial fetal membrane which is the last membrane that nutrients need to pass through before reaching fetal circulation. The endothelial fetal cells have major transporters that can indeed be the rate limiting steps to assess fetal nutrient flux. Based on the aforementioned reasons, it is necessary to appreciate that an alteration in placental membrane transporters does not necessarily translate to an equivalent alteration in nutrient flux unless the transporters are simultaneously changing on both syncytial membranes and on the endothelial fetal membrane. Placental functions and transport remain poorly understood especially in altered gestational conditions complicated by maternal obesity or other conditions. On a final note, although umbilical cord nutrient concentrations may resemble placental concentrations in some aspects, understanding the transport and mechanisms by which those concentrations are altered in the entity of placental membranes is crucial to isolate sites of impaired transport or metabolism and better target future treatments to limit adverse effects of maternal obesity.

## The effect of placental impaired function on offspring risk of disease

Efforts in research have been geared towards developmental origins of disease as risk of disease can be determined in utero and before implantation. In utero, the placenta is the major organ determining the passage of nutrients and oxygen to the fetus. Improper placentation or altered placental transport capacity can have a dire effect on the fetus. In addition to the probability of having inadequate placentation or altered placental function due to yet undetermined causes that may be of fetal or maternal origins, maternal obesity augments the inadequate conditions for the placenta to function or develop normally. Maternal obesity has been associated with fetal macrosomia, increased risk of childhood obesity, insulin resistance, type II diabetes , increased fetal adiposity, and other complications. Hence, the placenta is thought to be a crucial organ, despite its short lifespan, in determining fetal outcomes. The placenta is influenced directly by fetal nutrient needs and maternal supply at which placental function becomes impaired when the fetal needs and the maternal supply and signals are nonsynchronous or even inconsistent. Elevated maternal cortisol levels have additionally been shown to play a role in the augmented expression of placental corticosteroid 11-β-dehydrogenase isozyme 2 (HSD11B2) which inactivates cortisol thus allowing passage of active cortisol to the fetus. This is due to maternal stress and is associated with impaired fetal cognitive development. Overall, the maternal influence on the fetal development is manipulated by placental transport and metabolism.

## Discussing the mechanisms by which altered transport could affect susceptibility to chronic disease in the offspring

There has been a lot of focus on the mTORC pathway as it is a key activator in multiple pathways including glucose, amino acids and lipid metabolism. mTORC’s sensitivity to leptin and insulin has given it a lot of attention especially in maternal obesity where hyperinsulinemia and hyperleptinemia are usually detected. The altered activity of mTORC directly influences the metabolism and uptake of nutrients into the placenta. Activation of this pathway may be the underlying cause of macrosomia and increased fetal fat accretion, while its inactivation due to decreased maternal hormonal signals can underlie the growth-restricted fetal outcome. Despite the fact that maternal insulin does not cross the placental barrier, its downstream pathway including mTORC may increase fetal nutrient supply and elevate fetal insulin production. Activation of this pathway may lead to fetal pancreatic beta cell exhaustion and early maturation of pancreatic progenitor cells, which can also underlie a secondary cause of offspring insulin resistance. Furthermore, mTORC pathway causes increased de novo lipogenesis which leads to placental fat accretion that may have a deleterious impact on placental function. Some research has also focused on leptin and its placental receptor in obese mice. Due to maternal hyperleptinemia in obesity, the placenta exposed to high leptin levels may become leptin resistant. At term, placentas of obese mice had downregulated leptin receptors. The decreased leptin sensitivity evident by an increased activity of suppressor of cytokine signaling 3 (SOCS3) can be a leading cause of increased nutrient flux and fat accretion on the placenta ultimately impairing placental function.

Further research is still required in the field to elucidate the mechanisms by which the placental function is altered in obesity. Fully understanding the nutrient flux through the placental barriers to the fetal circulation is also necessary at all membrane loci. The current data paves the way for further research to be done especially with the advances in technology that may help replicate the human placental function accurately in normal and complicated pregnancies. Cell lines and animal studies remain indispensable for our overall understanding of the placental capabilities.

# References

Branum AM, Kirmeyer SE & Gregory ECW (2014). National Vital Statistics Reports Prepregnancy Body Mass Index by Maternal Characteristics and State: Data From the Birth Certificate, 2014. Available at: https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65\_06.pdf [Accessed December 8, 2017].

Catalano PM, Presley L, Minium J & Hauguel-de Mouzon S (2009). Fetuses of Obese Mothers Develop Insulin Resistance in Utero. *Diabetes Care* **32,** 1076–1080.

Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD & Ogden CL (2016). Trends in Obesity Among Adults in the United States, 2005 to 2014. *JAMA* **315,** 2284.

Gude NM, Roberts CT, Kalionis B & King RG (2004). Growth and function of the normal human placenta. *Thromb Res* **114,** 397–407.

Hales CM, Carroll MD, Fryar CD & Ogden CL (2015). Prevalence of Obesity Among Adults and Youth: United States, 2015–2016 Key findings Data from the National Health and Nutrition Examination Survey. Available at: https://www.cdc.gov/nchs/data/databriefs/db288.pdf [Accessed December 8, 2017].

Mingrone G, Manco M, Mora MEV, Guidone C, Iaconelli A, Gniuli D, Leccesi L, Chiellini C & Ghirlanda G (2008). Influence of maternal obesity on insulin sensitivity and secretion in offspring. *Diabetes Care* **31,** 1872–1876.

O’Reilly JR & Reynolds RM (2013). The risk of maternal obesity to the long-term health of the offspring. *Clin Endocrinol (Oxf)* **78,** 9–16.

Samuelsson A-M, Matthews PA, Argenton M, Christie MR, McConnell JM, Jansen EHJM, Piersma AH, Ozanne SE, Twinn DF, Remacle C, Rowlerson A, Poston L & Taylor PD (2008). Diet-Induced Obesity in Female Mice Leads to Offspring Hyperphagia, Adiposity, Hypertension, and Insulin Resistance: A Novel Murine Model of Developmental Programming. *Hypertension* **51,** 383–392.

Sebire N, Jolly M, Harris J, Wadsworth J, Joffe M, Beard R, Regan L & Robinson S (2001). Maternal obesity and pregnancy outcome: a study of 287 213 pregnancies in London. *Int J Obes* **25,** 1175–1182.