# 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. 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.

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. 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 pregnancy. The human placenta is composed of layers that have 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. Within those layers, various cell types exist and each has a specific role and maturation speed. Moving from the MVM to the BM, inwards from the maternal membrane to the fetal membrane, the cell types are as follows: extravillous cytotrophoblasts, syncytiotrophoblasts, villous cytotrophoblasts, cytotrophoblasts and fetal capillary endothelium (CHECK THE EXACT CELL TYPES SINCE YOU WERE GUNNA SAY STB 🡪 CTB 🡪ENDOTHELIAL FETAL 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 expected to be unique to each species. There is a number of differences between the human and animal placenta that include the difference in gestation age, litter size, maturation of the placenta, function of certain cell types in the placenta, differences in transporter expressions on the placental membranes, differences in interhemal layers and histological differences. The mouse placenta 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 (figure to show them) and besides having an endocrine function (hCG from sync CHECK IT EXACTLY), they are the main site of nutrient, gas and waste exchange between the mother and the fetus. The syncytiotrophoblast and the extravillous cytotrophoblasts (KNOW WHICH TB ARE ACTUALLY IN DIRECT CONTACT OR IS IT THE ENTIRE TB LAYER??) 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 placenta. 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. During the rest of the pregnancy, 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 trophoblast 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, 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 (CHECK IF SO) 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 human chorionic 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 function is overtaken by the placenta, specifically the syncytiotrophoblast. The definitive structure of the placenta in mice is determines almost halfway through gestation, whereas in humans, this 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 at rapid series of proliferation to produce the syncytiotrophoblast and cytotrophoblast layers. The syncytiotrophoblast begins its invasion of the maternal uterine wall invading the endometrium to allow for maternofetal interaction through spiral arteries. (ONE ARTICLE SAID IT IS THE CTB THAT INVADES THE MYOMETRIUM, WHEREAS ANOTHER SAID IT IS THE STB.. CHECK IT). 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 decidua, 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. 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. 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 divide to give rise to the 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 trophoblast invasion of the uterine wall occurs towards late gestation and is less critical in determining the survival of the fetus in the mouse, unlike the human trophoblastic invasion of the myometrium that dictates fetal supply and occurs very early in pregnancy.

## 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 are met, but it is additionally affected by maternal signals from the circulation.

Some studies have shown that insulin like growth factor-1 stimulates fetal nutrient uptake by the placenta 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 mTORC1 on the maternal side of the placenta causing its upregulation. In maternal obesity, the increased circulating maternal levels of insulin increase lipogenesis mediated by 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 it might be 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 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, 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. (CHECK ALL THE C/EBP THING).

Leptin in lean women stimulates system A function. In obese women, who may suffer from hyperleptinemia, system A function may be altered. 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.

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 uptake, is a mediator 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 apical membrane of the syncytiotrophoblast, the basolateral membrane of the syncytiotrophoblast and the fetal endothelial membrane before to reach the fetal circulation. The nutrient flux to the fetus depends on the circulating levels of maternal nutrients, the placental transporter and metabolic capacity, fetal requirements (CHECK IF SO) 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 limited or that the fetus depends less on glucose towards the late pregnancy stages. There is evidence showing that the placenta transforms the glucose to lactate to be used as a source of energy. (CHECK THIS OR ASK MOLLY)

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 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 fetus relies on maternal supply of cholesterol, as the fetal capacity to biosynthesize cholesterol develops in later pregnancy. 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.

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. <http://slc.bioparadigms.org/> FOR SLC TRANSPORTERS

<https://www.ncbi.nlm.nih.gov/books/NBK3/table/A145/> FOR ABC TRANSPORTERS

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.

## A recent study showed that 1,25-Dihydroxy vitamin D3 plays an important role in the placental amino acid transport through system A transport by upregulating the mRNA expression of 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 has been associated with suboptimal fetal growth and this could be attributed to vitamin D’s role in regulating the extracellular cytotrophoblast cell invasion of the uterus which determines access to maternal circulation (CHECK ALL OF THIS) (ADD THE NEW STUDY MENTIONED IN THE RATIONALE).

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, proton-coupled folate transporter, PCFT, allows for the transport of folate from the microvillous membrane to the basolateral membrane.

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 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. Active transport to the fetus

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 findings, 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.

Calcium in fetal circulations is regulated in a similar manner to adult circulations via parathyroid hormone 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, calcium transporters, are localized at both membranes of the syncytiotrophoblast, with calcium ATPase being primarily evident on the basolateral membrane. The rapid fetal development requires high amounts of calcium to 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. (WORTH KNOWING IF FETAL PTH CAN CASUE MATERNAL BONE RESORPTION OR NOT. IS FETAL PTH ONLY AFFECTING PLACENTAL CALCIUM TRANSPORTERS AND FETAL CALCIUM REGULATORY MECHANISMS?)

Inadequate maternal zinc levels 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. Endocytosis allows for the uptake of zinc by the placenta to be transported to the fetus but the mechanism are not fully understood (CHECK ZINC TRASNPORT ACROSS BASOLATERLA MEMBRANE AND ENDOTHELIALL FETAL CELLS?). Contrary to transferrin, zinc transporters show a reduced expression in vitro when maternal levels are high due to 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. Zinc levels are higher in the fetal circulation than in the maternal circulation.

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, apolipipoprotein 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 that microvillous membrane as they 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 (ASK DAVE ABOUT MEGALIN AND CHECK WHAT IT DOES EXACTLY).

## 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. In this review, we will focus on maternal obesity in the absence 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 SNAT1 and SNAT2 transporters 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 either an unaltered or increased system A transport.

Fatty acid and cholesterol transport in obesity

Emerging evidence shows that the fetal endothelial cells have a decreased transporter expression which may indicate that the rate-limiting step of fatty acid transport could be at the fetal side despite an upregulation in transporters at the syncytiotrophoblastic membrane.

Adiponectin supplementation may prevent the adverse outcomes of maternal obesity on the fetus.

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

Placentas collected from women with obesity had decreased amino acid transport system function and a reduced placental leptin sensitivity. Despite giving birth to normal-weight newborns, the alterations in placental

The upregulated amino acid transporters may be attributed to increased metabolic pathways upstream of amino acid uptake like placentla mammalian target of rapamycin, insulin and insulin-like growth factor, leptin, and adiponectin.

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

# Future directions

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

Data from human and rodent models may be similar but mechanistically different especially that the histology of the rodent and human placentas differs along with the differences in transporter expression, gestation period and multiple versus singleton pregnancy.

Need to assess the flux through endothelial fetal cells since they may be a rate-limiting step

An increase in transporters does not necessarily translate to an increase in flux as the last interhemal part is not thoroughly studied to determine guaranteed passage of nutrients and the full functions of the placenta especially under altered gestational conditions like obesity or other complications is not yet fully understood to determine placental

Although umbilical cord nutrient concentrations may resemble placental concentrations, understanding the transport and mechanisms by which those concentrations are alters are vital to assess impaired transport or metabolism.

* The effect of placental impaired function on offspring risk of disease
* Discussing the mechanisms by which altered transport could affect susceptibility to chronic disease in the offspring

mTORC

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