# 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 animal 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 GUNNSA SAY STB 🡪 CTB 🡪ENDOTHELIAL FETAL CELLS) .

Animal 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, one mononuclear trophoblast cell, 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.

**Overall endocrine function, barrier function, exchange of nutrients and gases/waste, aids in growth of the fetus through the endocrine function.**

The trophoblasts take up the most space in the placenta (figure to show them) and besides having an endocrine function (hCG from sync CHECK IT EXACTLY), they are the main site of nutrient and gas 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 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 determines whether the pregnancy will proceed. 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.

## Placental differentiation and growth processes throughout gestation

In humans, the trophoblast invasion of the endometrium determines the fetal survival. the trophoblasts invade the endometrium to allow for maternofetal interaction. 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 palcenta, the fetus is thought to acquire nutrients through the nutrient endocytotic action of the syncytiotrophblasts. The cytotrophoblasts tend to decrease after the first half of pregnancy.

Not only does the placenta have hormonal receptors that receive maternal signals from the circulation, but the placenta is also an active organ that secretes hormones to the maternal circulation. Placental secretions aim to increase the maternal catabolic signals to provide sufficient nutrition for the fetus in an attempt to adapt to the fetal growth rate and needs. This 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.

It seems like the cytotrophoblast differentiates into the syncytiotrophoblast but then at around 20 weeks of gestation, it disappears?

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

The placental transport of glucose does not rely on the circulating maternal insulin levels. 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. This ultimately causes increased lipogenesis mediated by mTORC1 signals and thus causes 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. 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, as adiponectin reduces the placental insulin sensitivity, it protects the fetus from the downstream upregulated insulin cascade which can 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.

Another signaling mechanism is C/EBP downstream of insulin. In obese women, it seems that CEBP is downregulated and its expression is decreased in syncytiotrophoblasts. Cytotrophoblasts that express C/EBP have a tendency to differentiate to STB in a normal placenta. Hence, the decreased C/EBP expression in cytotrophoblasts may be a protective mechanism maintaining the cytotrophoblasts in their initial state without further differentiation into STB. This could serve in decreasing the endocrine cfunction of the placenta which can mean that with increased obesity, the C/EBP pathway is less active in an effort to decrease STB hCG production. (CHECK ALL OF THIS and make more sense/ better wording)

# Altered placental transport capacity in obesity

* Key nutrient transporters present on the placental maternal and fetal membranes
* How micro- and macronutrient placental transporters are altered in obesity and how this affects nutrient flux and macronutrient accretion in the fetus
* Alterations in metabolic and signaling pathways that result in altered nutrient transport at the placental level
* 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
* 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

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