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.

This review will include the following sections:

# Introduction

* Associations between maternal obesity and offspring obesity and metabolic 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 three interhemal 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 that is on the fetal side and is in direct contact with the fetal endothelium and capillaries where the nutrient and oxygen 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: decidual cells, multinucleated cells, extravillous cytotrophoblasts, syncytiotrophoblasts, villous cytotrophoblasts, cytotrophoblasts and fetal capillary endothelium. Animal placenta, mainly that of mice and rats , has different cell structures but possesses the same discoid structure that the human placenta has. Due to differences in human and animal gestation periods, the placental growth and differentiation is expected to be unique to each. There is a number of differences between the human and animal placenta that include the difference in gestation age, 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.

* Placental differentiation and growth processes throughout gestation

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.

## 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.

# 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

# 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.