Effects of maternal obesity on placental function and fetal development

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Abstract

Obesity has reached epidemic proportions, and pregnancies in obese mothers have increased risk for complications including gestational diabetes, hypertensive disorders, pre-term birth and caesarian section. Children born to obese mothers are at increased risk of obesity and metabolic disease and are susceptible to develop neuropsychiatric and cognitive disorders. Changes in placental function not only play a critical role in the development of pregnancy complications but may also be involved in linking maternal obesity to long-term health risks in the infant. Maternal adipokines, i.e., interleukin 6 (IL-6), tumor necrosis factor alpha (TNF- α), leptin and adiponectin link maternal nutritional status and adipose tissue metabolism to placental function. Adipokines and metabolic hormones have direct impact on placental function by modulating placental nutrient transport. Nutrient delivery to the fetus is regulated by a complex interaction including insulin signaling, cytokine profile and insulin responsiveness, which is modulated by adiponectin and IL-1 β . In addition, obese pregnant women are at risk for hypertension and preeclampsia with reduced placental vascularity and blood flow, which would restrict placental nutrient delivery to the developing fetus. These sometimes opposing signals regulating placental function may contribute to the diversity of short and long-term outcomes observed in pregnant obese women. This review focuses on the changes in adipokines and obesity-related metabolic hormones, how these factors influence placental function and fetal development to contribute to long-term metabolic and behavioral consequences of children born to obese mothers.

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Introduction

Obesity currently affects approximately one-third of reproductive age women leading to a high prevalence of obesity in pregnancy (Flegal *et al.* 2012). Maternal obesity is associated with an increased risk for obstetrical complications such as gestational diabetes mellitus (GDM), gestational hypertension, preeclampsia, pre-term delivery and caesarian section (Sohlberg *et al.* 2012, Lim & Mahmood 2015, Lutsiv *et al.* 2015, Mission *et al.* 2015, MacInnis *et al.* 2016) and increased neonatal morbidity and mortality (Lim & Mahmood 2015, Marchi *et al.* 2015, Santangeli *et al.* 2015). In addition to adverse short-term outcomes, both the obese mother and her child are prone to develop cardiovascular, metabolic and neurological disorders later in life (LaCoursiere *et al.* 2010, Nguyen *et al.* 2015, Rivera *et al.* 2015, Stang & Huffman 2016).

Maternal obesity influences both placenta and the fetus, often resulting in fetal overgrowth and a greater frequency of large for gestational age (LGA) infants (Stang & Huffman 2016). Placental nutrient transport capacity has been shown to be increased in animal models of maternal obesity and is strongly associated

to birth weight in humans, providing mechanistic insight into the accelerated fetal growth associated with maternal obesity (Jones *et al.* 2009b, Jansson *et al.* 2013, Acosta *et al.* 2015, Rosario *et al.* 2015, Lager *et al.* 2016). Interestingly, non-branching placental angiogenesis has been reported in maternal obesity (Dubova *et al.* 2011). This finding may contribute to reduced placental blood flow found in hypertensive obstetric complications such as preeclampsia (Moran *et al.* 2015) in pregnancies complicated by obesity. As in lean women, hypertension in pregnancy and poor placental vascularity in maternal obesity are associated with fetal growth restriction rather than LGA.

Children born to obese mothers are more likely to develop childhood obesity and metabolic disease (Boney *et al.* 2005, Hermann *et al.* 2010, Santangeli *et al.* 2015), and this is especially true for those who were born LGA or macrosomic (>4 kg). Infants of obese mothers are prone to develop hyperinsulinemia and hypoglycemia in the neonatal period (Avci *et al.* 2015), which may, in part, be due to the development of GDM in some obese mothers (Desoye & van Poppel 2015). Animal studies have shown that maternal obesogenic diets

induce insulin resistance in the dam and increase fetal blood glucose levels leading to accelerated pancreatic β -cell maturation and impaired glucose tolerance in the offspring (Ford *et al.* 2009). Long-term studies have shown that children born to obese mothers also have increased susceptibility to develop neuropsychiatric and mood disorders (Bolton & Bilbo 2014, Rivera *et al.* 2015) and increased risk of cognitive impairments (Hinkle *et al.* 2012, 2013, Tanda *et al.* 2013, Adane *et al.* 2016). Thus, *in utero* exposure to maternal obesity programs the fetus for both metabolic and neuropsychiatric disease later in life, and recent studies indicate that placental function plays a critical role in linking intrauterine environment to long-term health risk (Heerwagen *et al.* 2010, Smith & Ryckman 2015, Dimasuay *et al.* 2016).

Given the high prevalence of obesity in pregnancy as a result of the current obesity epidemic worldwide, the adverse effects of maternal obesity for mother and child represent a major public health concern. However, although associations between obesity and maternal–fetal health are clear, the mechanisms linking the obese maternal environment to short- and long-term outcomes are complex and remain largely unknown. In this review, we will examine the changes in maternal adipokines and obesity-related metabolic hormones and how these factors influence placental function and fetal development, and may contribute to long-term health consequences of children born to obese mothers.

The impact of adipokines and metabolic hormones on placental function, fetal growth and development

Reproduction is tightly regulated by maternal energy balance, and adipokines play a significant role in creating a favorable environment for implantation and placental development (Reverchon *et al.* 2014, Dos Santos *et al.* 2015). During pregnancy, the placenta secretes cytokines and increases both the local and systemic levels, believed to be important in determining fetal allograft fate (Wedekind & Belkacemi 2016). The placenta produces an array of cytokines including tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6) and interleukin 1-beta (IL-1 β) (Hauguel-de Mouzon & Guerre-Millo 2006), which likely contribute to the elevation in circulating maternal inflammatory cytokines during pregnancy. Interestingly, cytokines may play distinct, yet significant, roles in placental development and function across gestation.

Maternal obesity has been associated with low-grade metabolic inflammation due to increased release of adipokines, which are believed to contribute to maternal glucose intolerance and insulin resistance and cardiovascular and neuroendocrine modulation associated with increased maternal BMI (Segovia *et al.* 2014). Increased cytokine and decreased adiponectin

release from adipose tissue has been linked to the meta-inflammatory state of obesity (Khodabandehloo *et al.* 2016, Luo & Liu 2016). Although the concept of low-grade inflammation with obesity is widely accepted, an increased pro-inflammatory cytokine profile in obese mothers has not been consistently reported and appears to be modulated with advancing gestation (Stewart *et al.* 2007, Friis *et al.* 2013, Christian & Porter 2014). A significant pro-inflammatory activation may not occur in the developing human fetus of obese mothers (Aye *et al.* 2014b, Pantham *et al.* 2015) or may be present only in severe obesity (body mass index >35 kg/m²) (Dosch *et al.* 2016). However, even if direct fetal exposure to maternal cytokines may be limited, cytokines in the maternal circulation have been proposed to modulate placental growth and function, which in turn influences fetal development.

TNF- α

In normal pregnancy, there is an increase in placental secretion of TNF- α and vascular endothelial growth factor (VEGF), which is believed to promote normal placental angiogenesis and growth (Pavlov *et al.* 2016). It has recently been discovered that TNF- α stimulates the production of a member of the VEGF family, placental growth factor (PlGF), in trophoblasts (Kato *et al.* 2016). TNF- α is a key regulator of implantation and trophoblast function in the first trimester and has been shown to induce apoptosis in cultured trophoblast cells (Knöfler *et al.* 2000, Pavlov *et al.* 2016, Siwetz *et al.* 2016). Thus, TNF- α appears to be important for trophoblast turnover and differentiation and overall placental development, a concept supported by the increasing maternal serum TNF- α levels across gestation (Christian & Porter 2014). However, reports of significantly elevated circulating TNF- α in obese compared to lean women are inconsistent (Stewart *et al.* 2007, Friis *et al.* 2013, Aye *et al.* 2014b, Christian & Porter 2014, Stone *et al.* 2014). Interestingly, TNF- α promotes apoptosis in villous trophoblasts from IUGR placentas compared to controls (Crocker *et al.* 2003). Intra-amniotic infusion of IL-1 β and TNF- α have been reported to induce pre-term labor in non-human primates (Sadowsky *et al.* 2006). Taken together, elevated TNF- α is critical for implantation, and normal placental development and variations found in TNF- α levels associated with maternal obesity may contribute to the diversity of obstetrical outcomes associated with this pregnancy complication.

IL-6

A number of studies report increased circulating levels of IL-6 in obese pregnant women as compared to women with normal BMI (Stewart *et al.* 2007, Christian & Porter 2014); however, this finding could not be confirmed by

all investigators (Stone *et al.* 2007, Aye *et al.* 2014b). Importantly, Friis and coworkers (Friis *et al.* 2013) demonstrated that maternal IL-6 was elevated early in pregnant obese mothers, but this difference was lost with advancing gestation. Low-grade inflammatory activation associated with maternal obesity may lead to increased placental nutrient transport capacity and promote fetal growth, because both IL-6 and TNF- α have been shown to stimulate placental System A amino acid transport (Jones *et al.* 2009a, Aye *et al.* 2015). Expression of the System A isoform sodium coupled neutral amino acid transporter 2 (SNAT2) was increased after IL-6 and TNF- α stimulation. IL-6 upregulated phosphorylation of signal transducer and activator of transcription 3 (STAT3) and using siRNA-mediated silencing of STAT3, it was demonstrated that STAT3 activation constitutes a critical mechanistic link between IL-6 and increased amino acid transport (Jones *et al.* 2009a). IL-6 also upregulates fatty acid uptake in human trophoblast cells, which would contribute to excessive fat deposition associated with babies born to obese mothers (Lager *et al.* 2011). TNF- α was found to mediate the upregulation of trophoblast System A through p38MAPK signaling, independent from the STAT3 pathway (Aye *et al.* 2015), demonstrating that pro-inflammatory cytokines regulate placental function by the activation of multiple signaling pathways.

Adiponectin

Adiponectin, an adipokine inversely correlated with insulin resistance, plays a crucial role in regulating immune responses, energy metabolism and placental insulin sensitivity (Ruan & Dong 2016). Lean women have higher adiponectin compared to obese women throughout pregnancy (Jansson *et al.* 2008), and maternal levels of adiponectin are inversely correlated with fetal growth, implicating a role for adiponectin in fetal development, metabolism and placental function (Aye *et al.* 2013, 2015, Duval *et al.* 2016). Adiponectin was shown to cause placental insulin resistance in cultured primary human trophoblast cells (Jones *et al.* 2010), which is in contrast to the insulin sensitizing effects of adiponectin in other tissues, including skeletal muscle (Liu *et al.* 2013). In trophoblasts, activation of PPAR α and increased transcription of ceramide synthase results in increased intracellular ceramide, inhibiting IRS-1 phosphorylation thereby reducing placental insulin responsiveness (Aye *et al.* 2014a). High adiponectin in lean women is therefore believed to limit placental nutrient transfer and fetal growth, in particular when insulin is high postprandially. In contrast, low circulating adiponectin in obese mothers will not effectively limit insulin's effect on placental function leading to increased placental nutrient transfer and fetal growth. The adiponectin/insulin interaction at the level of the placenta in lean and obese mothers is illustrated in Fig. 1A and B.

Figure 1 The role of adiponectin in lean and obese women to modulate fetal growth. (A) Adiponectin's influence on placental insulin response in lean mothers. Placental insulin signaling pathway in lean women where high levels of adiponectin leads to PPAR α activation and ceramide synthesis to decrease placental insulin responsiveness through IRS-1 inhibition limiting amino acid transport to modulate fetal growth. (B) Low maternal adiponectin in maternal obesity leads to fetal overgrowth. Low adiponectin in obese mothers allows for enhanced placental insulin sensitivity and activation of placental amino acid transport. This supports fetal overgrowth, which is associated with maternal obesity.

Maternal adiponectin has been shown to be a powerful regulator of placental function and fetal growth in normal and high-fat diet-induced obese pregnant mice (Aye *et al.* 2015, Rosario *et al.* 2015). Specifically, infusion of full-length adiponectin to normal pregnant mice results in downregulation of placental nutrient transport and fetal growth restriction (Rosario *et al.* 2012). Maternal infusion of adiponectin in obese dams normalized maternal insulin sensitivity, placental insulin/mTORC1 signaling, nutrient transport and fetal growth (Aye *et al.* 2015).

Placental nutrient transporter expression has been shown to be increased in human pregnancies complicated by obesity and is strongly correlated with birth weight. This relationship has been described for most macronutrients including glucose (Acosta *et al.* 2015), fatty acid (Lager *et al.* 2016) and amino acid

transporters (Jansson *et al.* 2013) in placenta from women of varying pre-gestational BMI. The underlying mechanisms for regulating the expression of these placental transporters are complex and not yet well understood. However, studies in mice suggest that improving maternal adiponectin levels in obese mothers may serve as an effective intervention strategy to prevent fetal overgrowth and the intrauterine transmission of obesity and metabolic disease to the next generation (Aye *et al.* 2015).

Leptin

Leptin regulates food intake and energy expenditure, and obese individuals have increased circulating leptin levels (Triantafyllou *et al.* 2016). Obesity is also associated with leptin resistance, impairing the ability of leptin to suppress appetite (Caro *et al.* 1996, Schwartz *et al.* 1996). Elevated maternal leptin modulates trophoblast invasion and nutrient supply, which could influence fetal growth (Tessier *et al.* 2013, Dos Santos *et al.* 2015). In the later stages of pregnancy when rapid fetal growth occurs, both insulin and leptin upregulate placental System A amino acid transport, to increase fetal nutrient availability (Jansson *et al.* 2003, Ericsson *et al.* 2005, von Versen-Höynck *et al.* 2009). Increased placental nutrient delivery as a result of altered maternal levels of metabolic hormones, such as leptin, in the maternal circulation has been proposed to contribute to fetal overgrowth in pregnancies complicated by obesity. Animal studies have demonstrated that offspring exposed to a premature neonatal leptin surge have increased number of hypothalamic nerve terminals and altered appetite regulation. In addition, these offspring show increased postnatal weight gain and develop obesity, suggesting an important role for early-life leptin in determining obesity later in life (Yura *et al.* 2005). Moreover, altered leptin signaling *in utero* may predispose the fetus for leptin resistance, which could explain the strong association between maternal obesity in pregnancy and obesity in children (Bouret 2012).

Placental Regulation

Although many factors contribute to human obesity, this review focuses on humans and studies using high-fat diet-induced obesity in animal models. High-fat/high-sugar diet-induced obesity increased placental amino acid and glucose transport to the fetus and was associated with the activation of placental insulin and mechanistic target of rapamycin (mTOR) signaling and fetal overgrowth (Rosario *et al.* 2015) in pregnant mice. Additionally, mTOR has been mechanistically linked to the regulation of placental nutrient transport in cultured primary human trophoblast cells. Specifically, mTOR signaling functions as a positive regulator of trophoblast

System A and L amino acid transporters (Rosario *et al.* 2013, 2016a,c) and folate transporters (Rosario *et al.* 2016b). In human pregnancy, placental mTOR is activated in pregnancies complicated by maternal obesity (Jansson *et al.* 2013) and inhibited in IUGR (Roos *et al.* 2007, Chen *et al.* 2015). These data suggest mTOR signaling is a master regulator of placental nutrient transport capacity and a powerful determinant of fetal growth.

Circulating maternal lipids serve as the source of fatty acids transported across the placenta and may also act as signaling molecules that modulate placental amino acid transporter activity through toll-like receptor 4 (TLR4) signaling (Lager *et al.* 2013). Carbon chain length and saturation are critical as monounsaturated fats, such as oleic acid (18:1, n-9), stimulates System A activity, whereas the anti-inflammatory omega 3 long chain polyunsaturated fatty acid, docosahexaenoic acid (DHA) inhibits the activity of this amino acid transporter (Lager *et al.* 2014). In normal pregnancy, TLR4 placental expression increases across gestation (Thaete *et al.* 2013) and TLR4 has been shown to be present in cytotrophoblasts and syncytiotrophoblasts (Mitsunari *et al.* 2006). Placental TLR4 expression has been reported to be elevated threefold to ninefold in obese mothers and is positively correlated to maternal and placental IL-6 expression (Yang *et al.* 2016). Similarly, in women with GDM, placental TLR4 expression is correlated with maternal hyperglycemia and insulin resistance (Feng *et al.* 2016). In liver, expression of TLR4 constitutes an important mechanistic link between high-fat diet/obesity and insulin resistance (Jia *et al.* 2014). Moreover, studies in pregnant sheep have demonstrated that inflammation is associated with maternal obesity and upregulates free fatty acid content in the cotyledon through TLR4 activation (Zhu *et al.* 2010a,b). Studies in human placenta likewise suggest that high maternal BMI promotes TLR4 signaling and propagation of inflammatory responses (Yang *et al.* 2016). These studies suggest that upregulated placental TLR4 expression may mediate placental inflammation and increased placental transfer of nutrients, including amino acids and fatty acids, thereby contributing to fetal overgrowth and/or increased fat deposition in pregnancies complicated by maternal obesity. The interactions of adipokines and insulin to regulate placental function are illustrated in Fig. 2.

Obstetric complications associated with maternal obesity

As compared to women with normal BMI, obese mothers have a markedly increased risk to develop GDM, as demonstrated by the high prevalence (33%) of obese pregnant women diagnosed with this complication (Farren *et al.* 2015). Infants of GDM mothers are at

Figure 2 Metabolic hormones and adipokine impact on placental function leads to fetal overgrowth. Factors associated with maternal obesity play a significant role in regulating placental transport and impact fetal development. Increased levels of TNF- α observed in pregnancies complicated by obesity stimulate the p38/MAPK pathway and high maternal leptin and/or IL-6 levels stimulate Systems A/L via STAT3 activation. Placental toll-like receptor 4 expression is increased in obese women who often have high non-esterified fatty acids leading to the activation of placental amino acid transport. High maternal insulin also activates mTOR-System A/L to increase amino acid transport, leading to fetal overgrowth.

increased risk for LGA (9–18%) and the risk is particularly high (22–35%) in obese mothers with GDM (Kim *et al.* 2014). Obese women are twice as likely to develop preeclampsia and six times more likely to develop gestational hypertension compared to normal weight women (Stang & Huffman 2016). Hypertensive obstetric complications are generally associated with small-for-gestational age neonates (SGA) (Stang & Huffman 2016). Additionally, there is an increased risk of stillbirth among obese mothers (Yao *et al.* 2016).

Gestational diabetes

Obese mothers with GDM are three times more likely to have LGA or macrosomic babies who have increased adiposity and are more likely to be delivered by caesarian section (Harper 2015, Logan *et al.* 2016). Moreover, GDM diagnosis is associated with increased future risk of obesity, cardiovascular disease and metabolic disease in both mother and child (Stang & Huffman 2016, Zhao *et al.* 2016). As discussed previously, maternal meta-inflammation (elevated IL-6, leptin and low adiponectin) may stimulate placental nutrient transport in pregnancies complicated by obesity with GDM contributing to fetal overgrowth (Segovia *et al.* 2014). Maternal TNF- α levels have been cited as a reliable predictor of insulin sensitivity during pregnancy (Kirwan *et al.* 2002) and TNF- α stimulates placental nutrient transport (Aye *et al.* 2015).

Maternal hyperglycemia and increased glucose transport capacity (Acosta *et al.* 2015) in obesity with GDM are factors believed to promote placental glucose transfer, causing fetal hyperinsulinemia and increased fetal growth (Palatianou *et al.* 2014, Desoye & van Poppel 2015). These changes are also likely to represent the underpinnings of hypoglycemia/hyperinsulinemia at

birth in infants of obese mothers (Palatianou *et al.* 2014, Desoye & van Poppel 2015). These studies suggest that placental function may be modulated by maternal glycemia, as well as obesity-related inflammation and that these factors are critical for determining the growth trajectory of the developing fetus.

Preeclampsia

In normal pregnancy, VEGF binds to its receptor, VEGF receptor 1 (Flt1), in the placenta to increase branching, angiogenesis and blood flow (Dubova *et al.* 2011). However, reduced placental VEGF–Flt1 interaction may explain enhanced non-branching placental angiogenesis in pregnancies complicated by obesity (Dubova *et al.* 2011). These changes have been proposed to result in a reduction *in utero*-placental perfusion leading to placental ischemia (Dubova *et al.* 2011). Placental hypo-perfusion increases the production of IL-6 and TNF- α (Pierce *et al.* 2000, Gadonski *et al.* 2006), perhaps contributing to reports of elevated maternal pro-inflammatory cytokines in some, but not all, obese women. Recent reports have suggested that placental IL-1 β expression increases with maternal BMI (Aye *et al.* 2014b). IL-1 β has been associated with preeclampsia and pre-term labor, where this cytokine is hypothesized to contribute to maternal endothelial dysfunction (Amash *et al.* 2012). IL-1 β expression has also been indicated as a mechanism to protect cytotrophoblasts from TNF- α cytotoxicity because IL-1 β downregulates the TNF receptor (Knöfler *et al.* 2000).

PlGF is a member of the VEGF family that binds primarily to the Flt1 receptor and remodels spiral arteries to allow for adequate blood supply to the placenta. Correlative studies have found that increased maternal soluble Flt1 (sFlt1) and decreased PlGF, along with

reduced PlGF in umbilical cord blood, are associated with reduced birth weight (Bergen *et al.* 2015). Elevated levels of sFlt1 sequester VEGF and PlGF to reduce their bioavailability for the membrane-bound receptors and therefore disrupts the angiogenic balance required for proper placental vascular remodeling and angiogenesis (Lecarpentier & Tsatsaris 2016). Preeclampsia is associated with increased maternal serum levels of sFlt1 and pro-inflammatory TNF- α (Spradley *et al.* 2015), which are linked to maternal hypertensive disorders and fetal growth restriction (Moran *et al.* 2015, Cetin *et al.* 2016). Rodent studies indicate that high-fat diets may impair the development of the placental vasculature as evidenced by increased hypoxia in the labyrinth, and fetal death was threefold higher in dams fed high-fat diets (Hayes *et al.* 2012). The pups that survived were often small for gestational age (Hayes *et al.* 2012).

Therefore, a critical distinction may be occurring between reduced placental vascularization, which would tend to decrease fetal growth vs stimulation of placental nutrient transfer, thought to accelerate fetal growth. These opposing signals may provide an explanation for the variation in fetal outcomes observed in pregnancies complicated by obesity. IL-1 β appears to be consistently associated with hypertensive disorders such as preeclampsia (Kalinderis *et al.* 2011, Dong & Yin 2014, Leme Galvão *et al.* 2016) and may be predictive of future disease in early-to-mid-pregnancy (Siljee *et al.* 2013, Taylor *et al.* 2016). Enhanced placental secretion may be the primary source of circulating IL-1 β (Amash *et al.* 2012). In Fig. 3, we have summarized key factors including maternal cytokine, lipid and metabolic hormone profiles that may interact in maternal obesity to cause diverse infant phenotypes at birth.

Long-term outcomes of children born to obese mothers

Maternal obesity propagates a vicious cycle of metabolic disorders passed down from mother to fetus *in utero*, with long-lasting impact on child and adult health. Children born to obese mothers have a two-fold increased risk for childhood obesity (Zhang *et al.* 2011). In addition, children born to obese mothers are at increased risk for metabolic, cardiovascular and neurological disorders later in life (LaCoursiere *et al.* 2010, Nguyen *et al.* 2015, Rivera *et al.* 2015, Stang & Huffman 2016). Pancreatic β -cell maturation is accelerated in the offspring of obese sheep (Ford *et al.* 2009). Early exposure to elevated glucose levels is believed to impair pancreatic function, predisposing the offspring for obesity and metabolic disease later in life through early onset of β -cell dysfunction (Armitage *et al.* 2004, 2005, Ford *et al.* 2009).

Long-term longitudinal and associative studies have shown that children born to obese mothers have an

increased risk to develop neuropsychiatric and mood disorders and increased risk of cognitive impairments (Hinkle *et al.* 2012, 2013, Tanda *et al.* 2013, Bolton & Bilbo 2014, Rivera *et al.* 2015, Adane *et al.* 2016). Animal models of high-fat diet-induced obesity demonstrate that offspring display social impairments, anxiety and depressive phenotypes with cognitive impairment and hyperactivity (Sullivan *et al.* 2015). Similarly, increased proliferation was observed in the fetal hypothalamus when exposed to high levels of IL-6 *in vivo* and *in vitro* (Kim *et al.* 2016). Elevated maternal TNF- α is associated with obesity (Atègbo *et al.* 2006, Aye *et al.* 2014b, Stone *et al.* 2014), pre-term birth and hyperlipidemia (Jelliffe-Pawlowski *et al.* 2014) and elevated TNF- α from cord blood of pre-term babies has been associated with cognitive deficits at 5 years of age (von Ehrenstein *et al.* 2012). Interestingly, 35% of children with autism also suffer from childhood obesity (Granich *et al.* 2016), further linking the *in utero* environment with a predisposition for both neurodevelopmental and metabolic disorders. The observed behavioral and cognitive deficits in children of obese mothers may be linked to alterations in the serotonergic system and hypothalamic–pituitary–adrenal (HPA) axis resulting from increased pro-inflammatory cytokines and high-fat diets (Ford *et al.* 2009, Sullivan *et al.* 2015, Kim *et al.* 2016).

The placenta has recently been identified as a critical source of serotonin for the developing fetus, where it plays a role during intrauterine life by modulating forebrain development (Bonnin *et al.* 2011). It has been suggested that pregnancy conditions such as maternal stress and inflammation upregulate placental serotonin production to program the developing fetus for neurodevelopmental disorders (St Pierre *et al.* 2015, Brummelte *et al.* 2016, Goeden *et al.* 2016). Increased IL-1 and IL-6 have been identified as potential cytokines linked to changes in placental function and subsequent neurodevelopmental insults that include forebrain damage and behavioral consequences in rodents (Smith *et al.* 2007, Girard *et al.* 2010). Importantly, serotonin neurotransmission is impaired in autism and schizophrenia and both disorders are linked to exposure to increased pro-inflammatory cytokines, such as IL-6 *in utero* (Atladóttir *et al.* 2010, Brown & Derkits 2010, Meyer *et al.* 2011). Recent studies found that maternal IL-6-mediated inflammatory responses influenced fetal neurodevelopment through upregulated conversion of maternal L-tryptophan to serotonin, leading to excess serotonin production by the placenta and blunted fetal forebrain axonal outgrowth (Goeden *et al.* 2016). Given that IL-6 plays a role in both nutrient delivery and serotonin synthesis, increased IL-6 associated with maternal obesity (Stewart *et al.* 2007, Friis *et al.* 2013,

Figure 3 Role of adipokines and metabolic hormones in pregnancies complicated by obesity. Diversity in cytokine profiles in obese women may contribute to variation in fetal growth outcomes. In pregnancies complicated by LGA, multiple metabolic factors, insulin, leptin, IL-6 and TNF- α and low maternal adiponectin have been found to stimulate placental nutrient transport, contributing to fetal overgrowth. In pregnancies complicated by hypertension, IL-1 β and sFlt1 are upregulated, whereas PlGF is decreased, leading to reduced placental blood flow, which will limit fetal growth. Fetal brain development and long-term neurodevelopmental programming are linked to inflammation and placental serotonin production. Interestingly, both poor and accelerated fetal growth are associated with similar long-term metabolic disorders in the children.

(Christian & Porter 2014) could significantly alter fetal serotonin balance and program life-long disease and neurocognitive disorders (Bolton & Bilbo 2014).

Similarly, leptin is a neurotropic factor and appears to be critical for hypothalamic development

(Bouret 2012) and long-term behavioral programming (Farr *et al.* 2015) in the offspring of obese mothers. Impaired metabolic regulation and leptin resistance in offspring of diabetic animals adversely influences the developing hypothalamus (Steculorum & Boret 2011,

López-Gallardo *et al.* 2015). Leptin deficiency with the loss of placental-derived leptin in growth restricted and pre-term delivered offspring contributes to reduced frontal cortex volume and behavioral deficits in rats (Dexter *et al.* 2014). Leptin is believed to impact fetal organ growth, including the brain, appetite regulation and cognition during early development (Briffa *et al.* 2015). Some authors have suggested that leptin replacement in early life may improve long-term metabolic and behavioral outcomes (Chen *et al.* 2011, Meyer *et al.* 2014).

Conclusion

In summary, although numerous cytokines (IL-6, TNF- α and leptin) as well as maternal insulin stimulate placental nutrient transporter activity, other adipokines (IL-1 β and adiponectin) inhibit insulin-stimulated nutrient transport. Therefore, multiple maternal adipokines are critical signaling molecules that link maternal nutrient status and adipose tissue metabolism to placental nutrient transport and in turn, impact fetal organ development and alter growth patterns *in utero*. A clear interaction between cytokine and insulin signaling has been demonstrated in trophoblast cells, but other factors such as maternal dietary fat intake likely influence placental function and are more difficult to quantify in pregnant women. Trophoblast mTOR signaling acts as a nutrient-metabolic sensor by responding to a wide diversity of upstream effectors to regulate expression and membrane trafficking of nutrient transporter proteins; however, other cellular signaling networks within the trophoblast are also involved such as PPARs, STAT3, NF κ B and p38 MAPK (Jones *et al.* 2009a, Aye *et al.* 2014a, 2015). Therefore, complexity in the regulation of trophoblast function overlays the diversity of maternal signals. Placental vascular development is likely independently regulated, but with similar inflammatory activators, leading to altered angiogenesis in some, but not all, obese women. Specific maternal cytokine profiles associated with particular clinical outcomes are yet to be established. Although important, these studies are difficult and are confounded by the multiple interactions between dietary diversity, maternal adipokines and insulin signaling at the level of the placenta, all of which contribute to the regulation of nutrient transport function, angiogenesis and likely fetal development.

Importantly, increased placental nutrient transport capacity and placental vascular development appear to have opposing regulatory roles in obese mothers. Nutrient transporter activation in obese and GDM mothers plays a significant role in fetal overgrowth. Reduced vascular branching in placentas of obese mothers with hypertensive disorders such as preeclampsia may be an underlying mechanism restricting fetal growth in those pregnancies. Given that obese mothers have significant diversity in fetal growth outcomes, it is important to

design effective studies throughout pregnancy to define unique combinations of factors including adipokines, insulin and angiogenic factors that lead to distinct phenotypes among neonates born to obese mothers. For each obese woman, a unique cytokine profile, insulin sensitivity and diet may contribute to determining the growth trajectory and long-term health of her child.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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