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, preterm 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 between insulin signaling, cytokine profile and insulin responsiveness, which is modulated by adiponectin and IL-1β. 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.

Keywords

maternal-fetal exchange; trophoblast; pregnancy complications; human; inflammation

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

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(GDM), gestational hypertension, preeclampsia, pre-term delivery and caesarian section (Mission et al. 2015; Sohlberg et al. 2012; Lim and Mahmood 2015; MacInnis et al. 2016; Lutsiv et al. 2015) and increased neonatal morbidity and mortality (Marchi et al. 2015; Santangeli et al. 2015; Lim and Mahmood 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 (Stang and Huffman 2016; Rivera et al. 2015; Nguyen et al. 2015; LaCoursiere et al. 2010).

Maternal obesity impacts both placenta and the fetus, often resulting in fetal overgrowth and a greater frequency of large for gestational age (LGA) infants (Stang and 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; Rosario et al. 2015, Jansson et al. 2013; Lager et al. 2016; Acosta et al. 2015). Interestingly, non-branching placental angiogenesis has been reported in maternal obesity (Dubova et al. 2011). This finding may contribute to reduce 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 and 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 (Rivera et al. 2015; Bolton and Bilbo, 2014) and increased risk of cognitive impairments (Adane et al. 2016; Hinkle et al. 2012; Hinkle et al. 2013; Tanda et al. 2013). 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 (Smith and Ryckman, 2015; Heerwagen et al. 2010; 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, while 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 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 (Dos Santos et al. 2015; Reverchon et al. 2014). During pregnancy, the placenta secretes cytokines and increases both the local and systemic levels, believed to be important in determining fetal allograft fate (Wedekind and 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-1β) (Hauguel-de Mouzon and 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, 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 and 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 (Friis et al. 2013; Stewart et al. 2007; Christian and 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/m^2) (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 impacts 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 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 and 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; Stone et al. 2014; Aye et al. 2014b; Christian and Porter 2014). Interestingly, TNF-α promotes apoptosis in villous trophoblasts from IUGR placentas compared to controls (Crocker et al.

2003). Intra-amniotic infusion of IL-1β 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 and Porter 2014), however this finding could not be confirmed by all investigators (Stone et al. 2007; Aye et al. 2014b). Importantly, Friis et al. (2013) demonstrated that maternal IL-6 was elevated in early 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 up-regulated 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 up-regulates 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 up-regulation of trophoblast System A through p38MAPK signaling, independent from the STAT3 pathway (Aye et al. 2015), demonstrating that pro-inflammatory cytokines regulate placental function through 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 and 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; Aye et al. 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 PPARα 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 Figure 1A and B.

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 (Rosario et al. 2015; Aye et al. 2015). Specifically, infusion of full-length adiponectin to normal pregnant mice results in down-regulation 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 expression of these placental transporters is 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 (Schwartz et al. 1996; Caro 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 up-regulate 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 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).

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 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. 2016a; Rosario et al. 2016c; Rosario et al. 2013) 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 placentas, 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 while 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 three to nine-fold 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 up-regulates free fatty acid content in the cotyledon through TLR4 activation (Zhu et al. 2010a; Zhu et al. 2010b). 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 up-regulated 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 Figure 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 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 and Huffman 2016). Hypertensive obstetric complications are generally associated with small for gestational age neonates (SGA) (Stang and 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 (Zhao et al. 2016; Stang and Huffman, 2016). As discussed above, 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 and van Poppel 2015). These changes are also likely to represent the underpinnings of hypoglycemia/hyperinsulinemia at birth in infants of obese mothers (Desoye and van Poppel 2015; Palatianou et al. 2014). 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 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 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-1β expression is elevated and increases with maternal BMI (Aye et al. 2014b). IL-1β has been associated with preeclampsia and preterm labor, where this cytokine is hypothesized to contribute to maternal endothelial dysfunction (Amash et al. 2012). IL-1β expression has also been indicated as a mechanism to protect cytotrophoblasts from TNF-α cytotoxicity because IL-1β down regulates 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 and 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 (Cetin et al. 2016; Moran et al. 2015). 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 three fold 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 versus 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-1β appears to be consistently associated with hypertensive disorders such as preeclampsia (Kalinderis et al. 2011; Dong and 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 of IL-1β (Amash et al. 2012). In Figure 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 (Stang and Huffman 2016; Rivera et al. 2015; Nguyen et al. 2015; LaCoursiere et al. 2010). 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; Armitage et al. 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 (Rivera et al. 2015; Bolton and Bilbo, 2014, Adane et al. 2016; Hinkle et al. 2012; Hinkle et al. 2013; Tanda et al. 2013). 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 (Stone et al 2014, Aye et al. 2014b; Atègbo et al. 2006), preterm birth and hyperlipidemia (Jelliffe-Pawlowski et al. 2014) and elevated TNF-α from cord blood of preterm 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 (Kim et al. 2016; Sullivan et al. 2015; Ford et al. 2009).

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 up-regulate placental serotonin production to program the developing fetus for neurodevelopmental disorders (St Pierre et al. 2015; Goeden et al. 2016; Brummelte 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* (Brown and Derkits, 2010; Atladóttir et al. 2010; Meyer et al. 2011). Recent studies found that maternal IL-6 mediated inflammatory responses impacted fetal neurodevelopment through up-regulated 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 (Christian and Porter, 2014; Stewart et al. 2007; Friis et al. 2013) could significantly alter fetal serotonin balance and program life-long disease and neurocognitive disorders (Bolton and 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 impact the developing hypothalamus (Steculorum and 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 (Meyer et al. 2014; Chen et al. 2011).

Conclusion

In summary, while numerous cytokines (IL-6, TNF-α and leptin) as well as maternal insulin stimulate placental nutrient transporter activity, other adipokines (IL-1β 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, NFκβ, p38 MAPK (Aye et al. 2014a; Jones et al. 2009a; Aye et al. 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. While 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 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.

Acknowledgments

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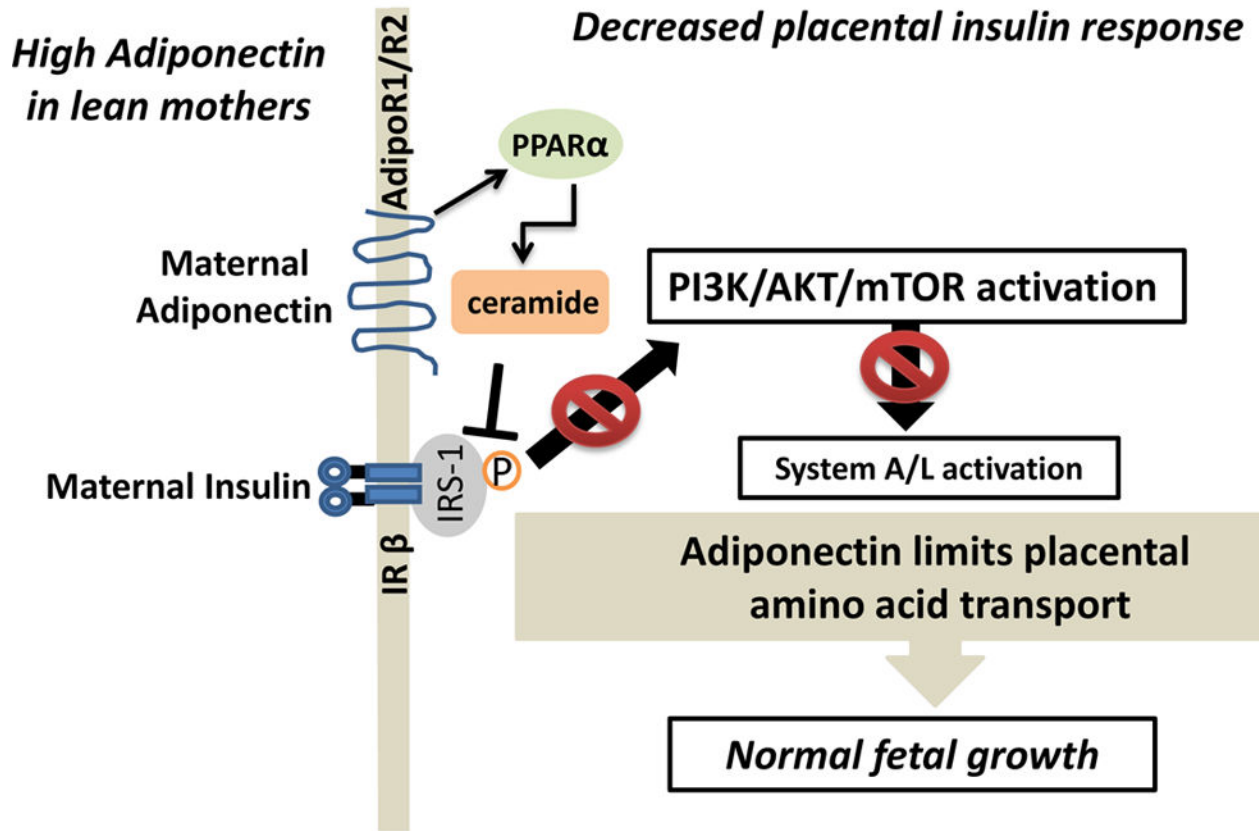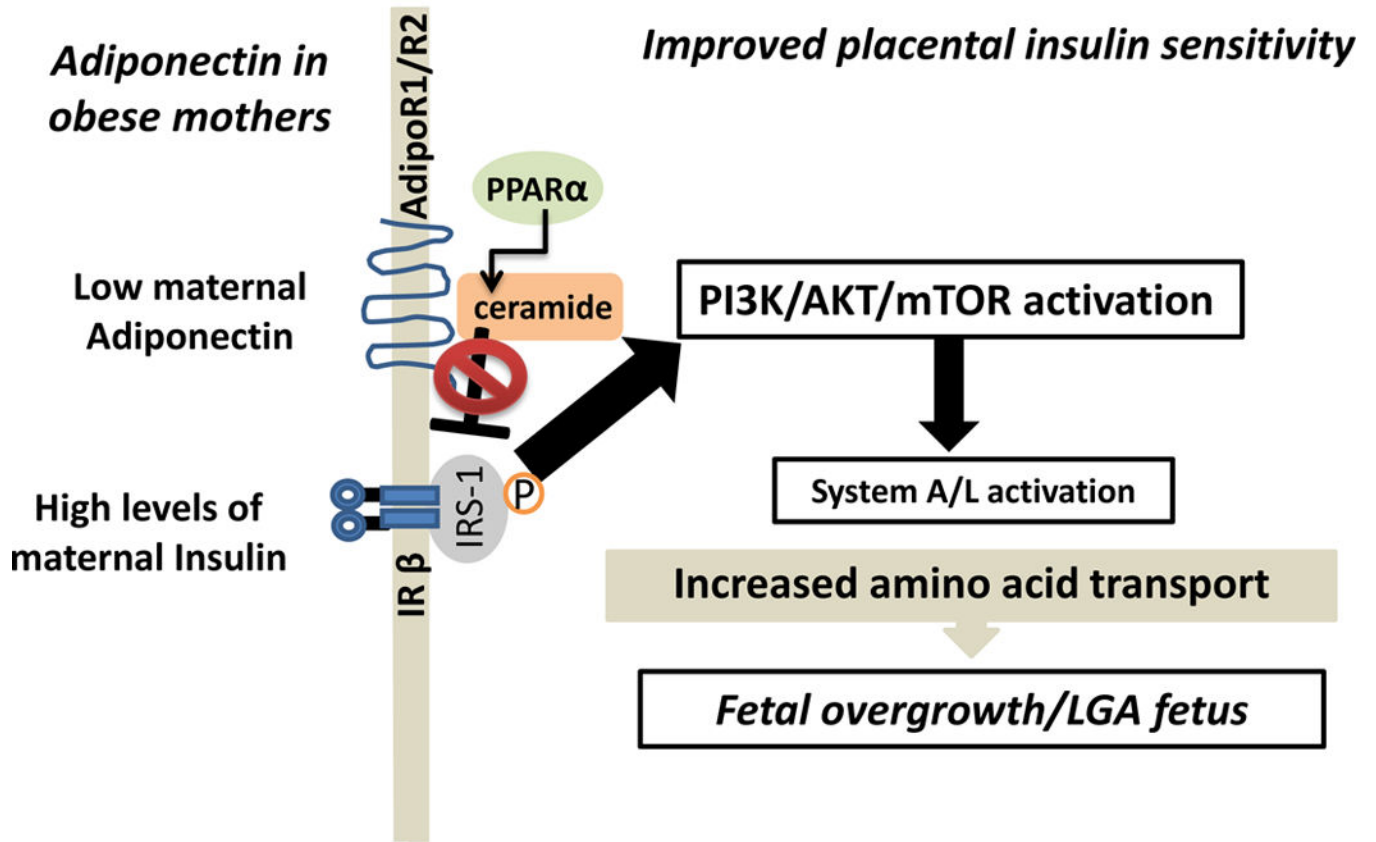
A.

High Adiponectin in lean mothers

Decreased placental insulin response

AdipoR1/R2

Maternal Adiponectin

PPARα

ceramide

PI3K/AKT/mTOR activation

Maternal Insulin

IRS-1

P

IR β

System A/L activation

**Adiponectin limits placental amino acid transport**

Normal fetal growth

Figure 1.
The role of adiponectin in lean and obese women to modulate fetal growth. (1A) Adiponectin influence on placental insulin response in lean mothers. Placental insulin signaling pathway in lean women where high levels of adiponectin leads to PPARα activation and ceramide synthesis to decrease placental insulin responsiveness through IRS-1 inhibition limiting amino acid transport to modulate fetal growth. (1B) Low maternal adiponectin in maternal obesity leads to fetal overgrowth. Low adiponectin in obese mothers allows for improved placental insulin sensitivity and activation of placental amino acid transport. This supports fetal overgrowth which is associated with maternal obesity
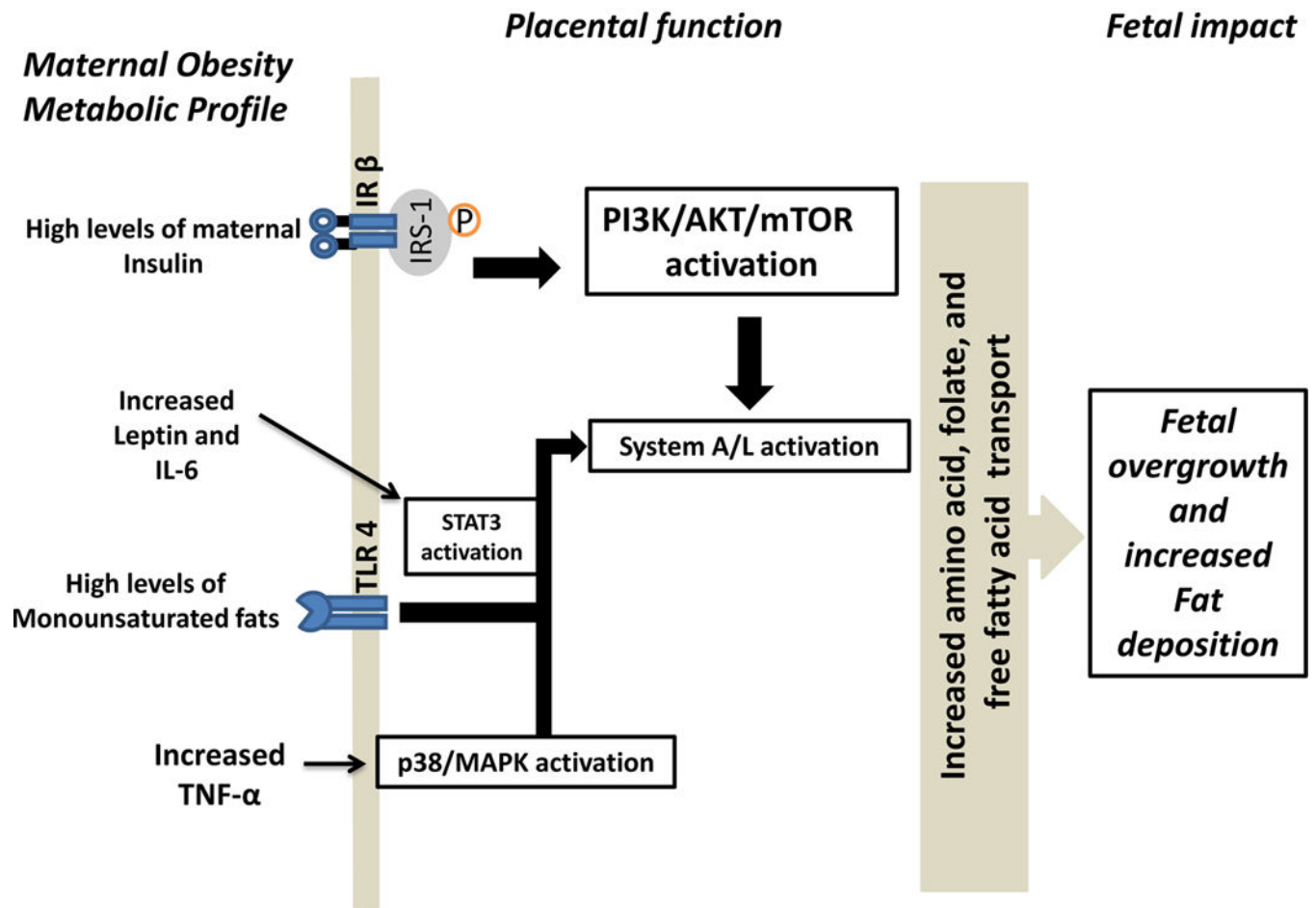
Figure 2.
Metabolic hormones and adipokine impact on placental function leads to fetal overgrowth.
Factors associated with maternal obesity play a significant role in regulating placental
transport and impact fetal development. Increased levels of TNF-α observed in pregnancies
complicated by obesity 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 activation of placental amino acid transport. High maternal insulin also activates
mTOR-System A/L to increase amino acid transport, leading to fetal overgrowth.
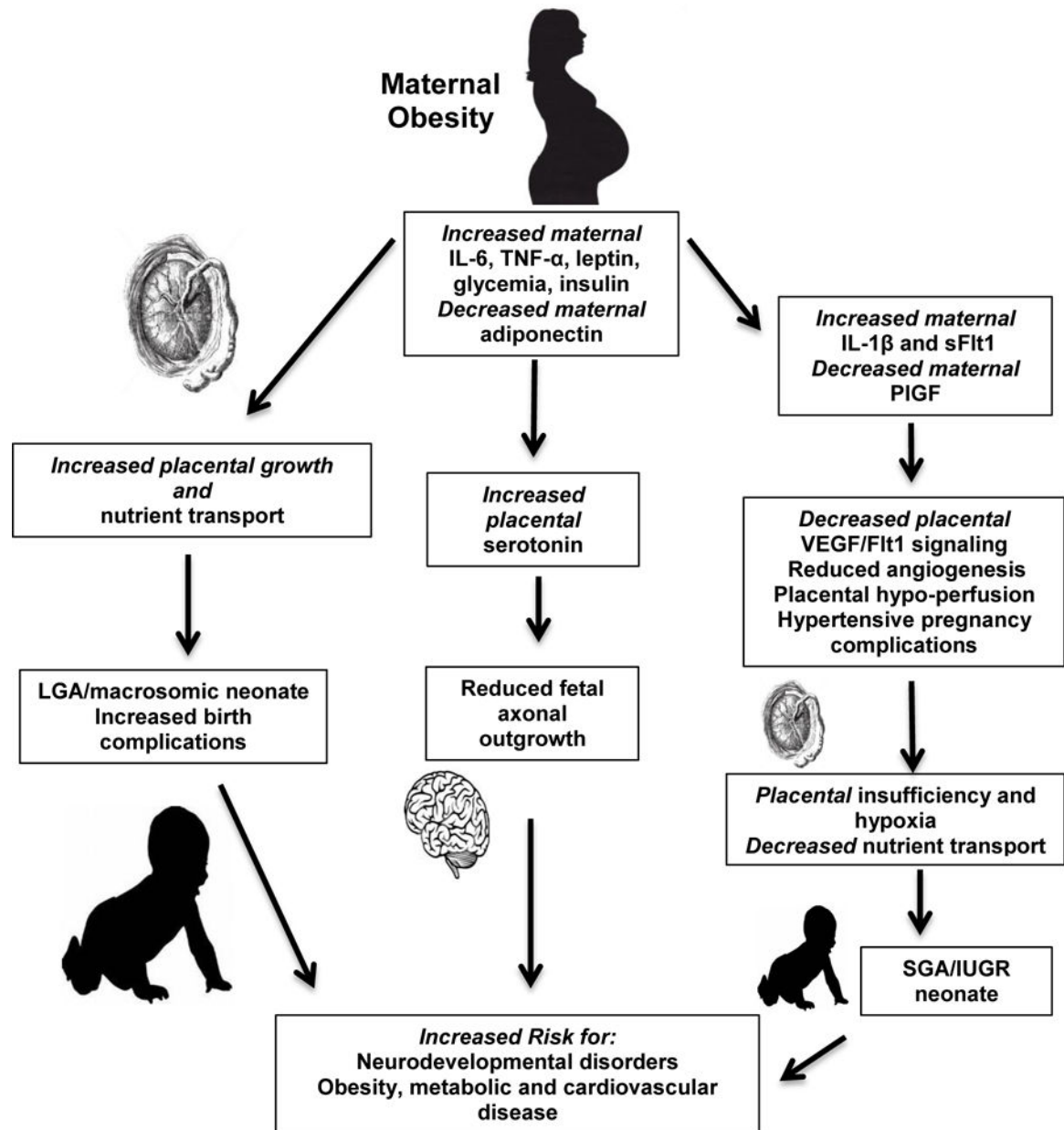
Figure 3.
Role of adipokines and metabolic hormones in pregnancies complicated by obesity.
Diversity in cytokine profiles in obese women may contribute to variation in fetal growth
outcomes. In pregnancies complicated by LGA, multiple metabolic factors, insulin, leptin,
IL-6 and TNF-α and low maternal adiponectin have been found to stimulate placental
nutrient transport, contributing to fetal overgrowth. In pregnancies complicated by
hypertension, IL-1β and sFlt1 are up-regulated while PlGF is decreased, leading to reduced
placental blood flow which will limit fetal growth. Fetal brain development and long-term
neurodevelopmental programming is 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