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Placental Function in Maternal Obesity

Amy C. Kelly[1], **Theresa L. Powell**[1,2], **Thomas Jansson**[1]

[1]Division of Reproductive Sciences, Department of Obstetrics and Gynecology, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, United States

[2]Department of Pediatrics, Section of Neonatology, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, United States

Abstract

Maternal obesity is associated with pregnancy complications and increases the risk for the infant to develop obesity, diabetes and cardiovascular disease later in life. However, the mechanisms linking the maternal obesogenic environment to adverse short- and long term outcomes remain poorly understood. As compared with pregnant women with normal BMI, women entering pregnancy obese have more pronounced insulin resistance, higher circulating plasma insulin, leptin, IGF-1, lipids and possibly proinflammatory cytokines and lower plasma adiponectin. Importantly, the changes in maternal levels of nutrients, growth factors and hormones in maternal obesity modulate placental function. For example, high insulin, leptin, IGF-1 and low adiponectin in obese pregnant women are expected to activate mTOR signalling in the placenta, promoting protein synthesis, mitochondrial function and nutrient transport. These changes are believed to increase fetal nutrient supply and contribute to fetal overgrowth and/or adiposity in offspring, which increases the risk to develop disease later in life. Interventions that specifically target placental function, such as activation of placental adiponectin receptors, may prevent the transmission of metabolic disease from obese women giving birth to large babies to the next generation. The majority of obese women give birth to normal sized infants and these pregnancies are associated with activation of inflammatory signalling pathways, oxidative stress, decreased oxidative phosphorylation and lipid accumulation in the placenta. Recent bioinformatics approaches expand these alterations to include novel targets, however how placental changes in obese women giving birth to normal sized babies are linked to poor short and long-term infant outcomes is unclear.

Keywords

Maternal-fetal exchange; syncytiotrophoblast; placental transport; fetal growth; human; fetal development

Corresponding Author Information: Amy C. Kelly, PhD, University of Colorado Denver, OB/GYN Reproductive Science Division; Mail Stop 8613, 12700 East 19th Avenue, P.O. Box 6511, Aurora, CO 80045, Phone 303 724 1653, Amy.Kelly@CUAnschutz.edu.

Author Contribution

A.C.K. wrote the manuscript. T.L.P and T.J. were involved in the planning, organization and revision of the review.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations: Gene abbreviations adhere to the HUGO Gene Nomenclature Committee recommendations

Introduction

High body mass index (BMI) is increasingly prevalent in reproductive aged women around the world. For example, almost 2/3 of American women now enter pregnancy either overweight (BMI 25 – 29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2; (1–3)). Maternal overweight in pregnancy is associated with adverse short- and long-term outcomes (4–6), however reports in the literature have predominantly addressed maternal obesity, which will be the focus of this review. Pregnancies complicated by obesity are associated with an array of obstetric complications, including gestational diabetes and preeclampsia that increase infant morbidity and mortality (7,8). Infant adverse outcomes include fetal overgrowth, altered body composition, and neural tube defects (4,9–11). The long-term consequences of maternal obesity in offspring are well documented and include an increased risk to develop cardiovascular disease, metabolic syndrome, diabetes, cancer, and psychiatric disorders (12–18). The strong association between maternal obesity and metabolic syndrome in childhood is of particular concern because it creates a vicious, detrimental cycle of intrauterine transmission of metabolic disease from the mother to her children (17–19). Thus, maternal obesity in pregnancy is a daunting public health problem with a profound impact on the health of the next generation.

Maternal obesity is associated with characteristic changes in circulating levels of nutrients, hormones, growth factors, cytokines and inflammatory mediators, including elevated lipids, leptin and IL-6 and low adiponectin levels. However, the mechanisms linking this ‘obesogenic’ metabolic environment to adverse short- and long-term fetal outcomes remain elusive. It is likely that increased levels of, for example, glucose and lipids in the maternal circulation are transmitted across the placental barrier, leading to fetal hyperglycemia and hyperlipidemia, which may adversely affect the developing fetus. In addition, placental function is regulated by an array of maternal metabolic signals (20,21) many of which are influenced by maternal obesity. Therefore, emerging evidence indicates that maternal obesity causes extensive changes in placental function, which have been suggested to mediate the adverse effects of maternal obesity on fetal development.

This review will focus on recent work determining the impact of obesity in human pregnancy on placental function. Experimental data in relevant animal models will be briefly discussed when providing compelling mechanistic insights. After introducing the short- and long-term consequences of maternal obesity in pregnancy and the characteristic metabolic alterations associated with this condition, we will summarize the findings from recent studies employing ‘omics’ approaches in placentas from obese women and review changes in placental signaling, metabolism and nutrient transport in response to maternal obesity. The review makes the distinction between obese women giving birth to large for gestational age (LGA) infants and maternal obesity associated with delivering an appropriate for gestational age (AGA) infant for several reasons. First, the evidence for adverse metabolic and cardiovascular long-term outcomes is more compelling for large LGA infants born to obese mothers than AGA infants of obese mothers. Second, changes in placental function in obese women delivering LGA infants are likely distinct as compared to obese women delivering AGA babies. Third, Whereas developing a model linking maternal obesity, changes in placental function, fetal overgrowth and long-term adverse consequences

is relatively straightforward, it is less clear how placental changes in obese women giving birth to normal sized babies are linked to poor short and long-term infant outcomes. Finally, we will identify priority areas for future studies and speculate on novel strategies for interventions targeting the placenta to prevent poor infant outcomes in pregnancies complicated by obesity.

The Clinical Problem of Maternal Obesity

The prevalence of obesity has increased markedly around the world over the past several decades. In France, one in five women of childbearing age is overweight, and about 15% of women are obese (22). In the United Kingdom and the United States, more than 30% of reproductive age females are obese and another 5% have severe obesity (BMI ≥40) (23,24). The prevalence of obesity also differs in regional and ethnic populations (23,25,26). For example, in the US, over 50% of African-American adults are reported to be obese whereas the prevalence of obesity in Asian-Americans is ~10% (22,25).

As in non-pregnant obese individuals, obesity in pregnancy is associated not only with marked hyperinsulinemia and dyslipidemia but also with impaired endothelial function, higher blood pressure, and low grade-inflammation (27). Maternal obesity increases the risk for pregnancy complications such as gestational hypertension, preeclampsia, stroke, venous thromboembolism, gestational diabetes, and caesarian delivery (6,11,28). Obesity in pregnancy also has a detrimental impact on the health of the offspring. Short-term adverse fetal outcomes in infants of obese mothers include increased risk of fetal overgrowth, still birth (29) and neonatal hypoglycemia (30). Fetal overgrowth is a major contributor to the increased rates of caesarian delivery as well as complications during delivery such as shoulder dystocia (31,32). Severe neonatal hypoglycemia affects 10–15% of newborns and has been associated with neurodevelopmental sequelae (30). In maternal obesity neonatal hypoglycemia is typically transient and stems from maladaptive, persistent hyperinsulinemia initiated by higher glucose concentrations *in utero* (33). Fetal hyperinsulinemia, measured by proxy in cord blood at delivery, is positively correlated with birth weight and neonatal adiposity but is inversely associated with weight gain up to 2 years of age, particularly in girls (34). Similarly, umbilical cord C-peptide levels are inversely associated with infant weight gain over the first year of life in girls, but not in boys (35). These data demonstrate that maternal obesity disrupts the normal transition in glucose metabolism occurring at birth and suggests that the effect of maternal obesity on offspring risk to develop obesity in childhood is influenced by infant sex.

In addition to the short-term consequences of maternal obesity on maternal and fetal health, infants of obese mothers are more likely to develop a range of health problems later in life, which has been reviewed extensively (5,36). For example, children of obese mothers have an increased risk for developing asthma (37) and neurocognitive disorders (38,39). In addition, maternal obesity, in particular if the infant is large-for-gestational age, is associated with the development of obesity and type-2 diabetes in childhood (14,19), perpetuating a vicious cycle where obese mothers transmit metabolic disease to future generations, and their daughters further propagate the disease to their children. Disease risk persists across the lifespan with strong associations between exposure to maternal obesity in pregnancy and

adult chronic inflammatory disorders (40,41), metabolic syndrome (42), diabetes (43), and hypertensive/cardiovascular disease (16).

Metabolism and Hormone Levels in Maternal Obesity

Maternal metabolism adapts to normal pregnancy to allow for the allocation of nutrients for placental and fetal growth. This carefully regulated metabolic adaptation is perturbed when the mother is obese resulting in a less optimal 'metabolic environment' that is likely linked to changes in placental function, fetal growth and development. The characteristic metabolic phenotype of women who enter pregnancy obese is related to glucose and lipid homeostasis, metabolic hormones and inflammatory mediators.

Glucose Metabolism

Glucose is the primary substrate for placental and fetal energy metabolism and normal pregnancy induces marked changes in maternal glucose metabolism, including insulin resistance, activation of hepatic glucose production and increased β-cell insulin release with higher plasma C-peptide (44), to promote placental and fetal glucose delivery. Obese women have 50-60% higher postprandial insulin concentrations than normal weight women in both early and late gestation (45). In addition, obese women are more glucose intolerant than pregnant women with normal BMI, as reflected by higher fasting, 1-hour and 2-hour glucose levels following an oral glucose tolerance test (OGTT) (45). Indeed, albeit not meeting the criteria for GDM, the abnormal response to OGTT in obese women is associated with the risk of delivering a LGA infant (46). Increased adiposity persists throughout the lifespan with increased frequency of high BMI in children of obese mothers. Interestingly, maternal pre-pregnant BMI is a stronger predictor for childhood obesity than gestational diabetes (47).

Lipids

While circulating lipids are well known to be elevated in pregnancy in all women, maternal obesity is associated with an altered maternal lipid profile (48). As compared to pregnant women with normal pre-pregnancy BMI, maternal obesity is associated with lower high-density lipoprotein (HDL) levels in first trimester and higher maternal triglyceride (TG) levels in the second and third trimesters. In addition, near term obese women have lower cholesterol and low-density lipoprotein (LDL) levels than women with normal pre-pregnancy BMI (27,49,50). TGs are hydrolyzed to non-esterified (free) fatty acids (NEFA) which are also elevated in maternal plasma throughout gestation in pregnancies complicated with obesity (48). In addition, high maternal TG levels in late pregnancy are associated with an increased risk of delivering a LGA infant (51).

Adipokines

Maternal obesity is associated with characteristic changes in the release of adipokines such as leptin and adiponectin, which have systemic effects on metabolism and energy homeostasis (52,53). Obese women have lower plasma adiponectin levels than normal BMI women throughout pregnancy (27,54–57) and maternal adiponectin is inversely correlated with maternal fat mass, insulin resistance, and glucose production as well as

with fetal growth, implicating a role for adiponectin in regulation of maternal metabolism, placental function, and fetal development (54,58,59). Leptin regulates satiety and energy expenditure and, as in non-pregnant individuals, circulating levels of leptin are elevated in obese pregnant women (60). Leptin is positively correlated with both maternal insulin concentrations and BMI in the first and third trimester and with BMI at term (54,57). Furthermore, maternal leptin levels correlate positively to fetal circulating leptin concentrations, and elevated cord leptin levels have been linked to fetal insulin resistance (52,61).

Growth Factors

Insulin-like-growth factors (IGFs) promote protein and carbohydrate metabolism and regulate fetal growth (62). The IGF system consists of IGF-1 and IGF-2, their six binding proteins (IGFBPs), and receptors. Maternal circulating IGFs predominantly originate from the liver and are, to a large extent, bound to IGFBPs (63). In early and late pregnancy, maternal IGF-1 is positively correlated and circulating IGFBP-1 concentrations are inversely correlated to maternal BMI (54,64). At term, cord concentrations of IGFBP-1 and IGFBP-6 are lower (65) in obese compared to lean women. Maternal IGF-1 was positively correlated and IGFBP-1 was inversely correlated to birth weight in infants from obese mothers (66).

Pro- and Anti-inflammatory Cytokines

In normal pregnancy, most inflammatory cytokines in the maternal circulation increase across pregnancy, in part due to cytokine secretion by the placenta (25). Numerous investigators have reported that maternal obesity further increases plasma concentrations of pro-inflammatory cytokines such as IL-6 (27), TNF-α (10), monocyte chemoattractant protein 1 (MCP-1) (68), IL-8, and C-reactive protein (10,27), supporting the concept that the mild pro-inflammatory state associated with normal pregnancy is exacerbated in maternal obesity. However, the literature is not consistent with a number of reports finding no significant elevation in circulating maternal cytokine levels in obese pregnant women as reviewed by Pendeloski and coworkers (69). There are a multitude of potential reasons for these discrepancies. However, the inconsistency in this data suggests that heightened inflammation is not a general phenomenon in pregnancies complicated by obesity but may occur in specific subgroups of obese women. The biological effects of pro-inflammatory cytokines are balanced by anti-inflammatory cytokines, such as interleukin (IL)-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11 and IL-22 (70). Although the effect of obesity on the levels of anti-inflammatory cytokines remains to be fully established, it has been suggested that a lack of the normal increase in IL-10 contributes to a pro-inflammatory environment in obese women (71).

The Human Placenta

The human placenta develops from fetal trophectoderm, which differentiates into trophoblast, and extraembryonic mesoderm, from which fibroblasts, endothelial cells, and macrophages in the villous core develop. As illustrated in Figure 1, the functional unit of the human placenta is the trophoblast villous tree, containing fetal blood vessels and covered by the syncytiotrophoblast, which is directly exposed to maternal blood entering the intervillous

space from the spiral arteries (72). There are three subtypes of trophoblast cells in the human placenta; cytotrophoblasts, extravillous trophoblasts and the syncytiotrophoblast (73). Cytotrophoblast cells either undergo fusion to form the multinucleated syncytiotrophoblast or differentiate into extravillous trophoblasts, which invade the spiral arteries in the decidua and myometrium. Trophoblast invasion into the spiral arteries is believed to be critical for the normal gestational increase in utero-placental blood flow by replacing the endothelial cells and degrading smooth muscle in the vessel walls (74,75).

The syncytiotrophoblast is the transporting and hormone producing epithelium of the human placenta. At term, the syncytiotrophoblast and the fetal capillary endothelium are the only largely continuous cell layers between maternal and fetal blood (Figure 1). Because the fetal-placental capillary endothelial cells allow a relatively unrestricted transfer of small molecules such as glucose and amino acids through intercellular junctions, the syncytiotrophoblast represents the primary barrier for movement of most solutes from the maternal to the fetal circulations. Specifically, transfer across the two polarized plasma membranes of the syncytiotrophoblast, the apical or microvillous plasma membrane (MVM) directed toward maternal blood in the intervillous space and the basal plasma membrane (BM) facing the fetal capillaries constitute the limiting steps for net flux from maternal to fetal circulations (Figure 1). Maternal-fetal exchange of many nutrients and ions occurs by mediated transfer involving transporter proteins expressed in the syncytiotrophoblast plasma membranes.

Maternal Factors Altered by Obesity Regulate Placental Function

Many maternal metabolites, hormones, growth factors and cytokines that are altered in maternal obesity have well established effects on placental function and may mediate the effects of maternal obesity on the placenta.

Insulin

Maternal obesity is associated with hyperinsulinemia and insulin activates placental glucose (76,77) and System A amino acid transporters (77–80). Importantly, despite peripheral insulin resistance, the placenta appears to maintain normal insulin responsiveness in maternal obesity (81). Therefore, the hyperinsulinemia that maintains euglycemia in the face of increasing insulin resistance in obese pregnant women is likely to have significant effects on placental growth and function. For example, if the placental insulin sensitivity is unaffected in maternal obesity as recently reported (81), elevated maternal insulin levels are expected to activate placental insulin and mTOR signaling as well as glucose and amino acid transport.

Adipokines

Maternal obesity is associated with low plasma adiponectin and elevated levels of leptin, changes that are believed to influence placental function and fetal growth (54,59). Leptin promotes placental lipolysis without affecting lipid synthesis (82), potentially resulting in decreased placental TG and cholesterol levels in pregnancies complicated by maternal obesity. In addition, leptin increases system A amino acid transport activity in villous

fragments (78,83) and stimulates the release of IL-6, nitric oxide, and human chorionic gonadotrophin in cultured primary human trophoblast cells (78,83). Adiponectin decreases amino acid uptake in term primary human trophoblast cells (84,85). Adiponectin also decreases the gene expression of glucose and System A amino acid transporters in first trimester primary trophoblast (86). Animal experiments demonstrate that adiponectin has similar effects on placental function *in vivo*. For example, chronic administration of adiponectin in normal weight pregnant mice inhibits placental function, including nutrient transport, and results in intrauterine growth restriction (87). In contrast, low maternal adiponectin, as observed in maternal obesity, is expected to promote placental nutrient transport. A mouse model of maternal obesity in pregnancy, characterized by low maternal adiponectin levels, increased placental insulin signaling and nutrient transport and fetal overgrowth (88) has provided direct evidence to support this hypothesis. Specifically, chronic infusion of adiponectin in obese dams, in rates that increased adiponectin levels to those observed in normal pregnant mice, normalized placental insulin and placental nutrient transport and fetal growth (58). These findings were recently confirmed in elegant studies in which knockdown of the maternal adiponectin gene causing lower circulating levels resulted in increased fetal growth (89,90).

Growth Factors

Maternal obesity has been reported to be associated with increased concentrations of IGF-1 in the maternal circulation (91), which may influence placental development and function. IGF-1 promotes trophoblast proliferation (92) and stimulates glucose transport across a monolayer of BeWo cells, a human choriocarcinoma cell line, by increasing the expression of glucose transporter 1 (GLUT1) in the BM (93). Moreover, IGF-1 increases glucose and amino acid uptake in cultured first trimester primary human trophoblast cells (94). Increased maternal IGF-1 bioavailability (high IGF-1 and low IGFBPs) in obese mothers may therefore promote placental nutrient uptake and transfer to the fetus.

Pro-inflammatory Cytokines

Specific cytokines have been shown to be elevated in the maternal circulation of obese mothers, in particular IL-6 (95,96) and TNF-α (10) and a positive correlation between maternal IL-6 and neonatal fat mass has been demonstrated (96), potentially mediated by effects on placental function. These two cytokines have been studied in cultured trophoblast cells and found to influence key placental functions including lipid and amino acid transport as well as placental metabolism. TNF-α activated phospholipase A2 (PLA2G2A) in cultured primary human trophoblast cells (97). Moreover, placental *PLA2G2A* expression was found to be increased in maternal obesity and associated with neonatal adiposity and it was proposed that PLA2G2A stimulation by TNF-α and leptin represents a key mechanism to favor excess fetal fat accretion (97). Incubation of primary human trophoblast cells with TNF-α and IL-1β decreased Slit2 expression, which is mechanistically linked to increased secretion of IL-6 and IL-8 and elevated expression of matrix metallopeptidase 9 (MMP-9; (98)). Using primary human trophoblast cells, Jones and co-workers reported that IL-6 stimulates system A amino acid transporter activity mediated by STAT3 signaling and increased expression of SNAT2 (99,100).TNF-α also stimulates System A amino acid transport in primary human trophoblast cells mediated by p38 MAPK signaling

(99,100). However, other cytokines likely have the opposite effect because conditioned media from monocyte/*P. falciparum*-infected erythrocyte co-culture, which contains an array of cytokines, inhibited System A amino acid uptake in primary human trophoblast cells (101). Furthermore, using the same experimental system Liong and co-workers reported that the pro-inflammatory agents lipopolysaccharide (LPS) endotoxin and the viral mimetic polyinosinic:polycytidylic acid (poly(I:C)) decreased the activity of the trophoblast insulin signaling pathway and glucose uptake but increased expression of SNAT1 and 2 and System A uptake of amino acids (102). Finally, some evidence suggests that IGF-I/insulin hybrid receptors are present in cultured primary human trophoblast cells and placenta (103,104) and that TNF-a inhibits the signaling associated with this receptor (104), providing a potential mechanisms by which TNF-a may inhibit insulin actions on the trophoblast. Collectively, these data suggest that, albeit pro-inflammatory cytokines have powerful effects on placental function, the specific effects differ between cytokines and their role in pregnancies complicated by maternal obesity is not yet clear.

Lipids

The effects of fatty acids on trophoblast cells depend on chain length and/or saturation. For example, physiological levels of oleic acid (18:1, OA) stimulate mTOR signaling and System A amino acid uptake in cultured primary human trophoblast cells mediated by toll-like receptor (TLR) 4, whereas the long chain polyunsaturated fatty acid, docosahexaenoic acid (22:6, DHA), had the opposite effect (105). Moreover, OA increased the expression of the lipase coactivator alpha-beta hydrolase 5 CGI-58 and perilipin-2 (PLIN2) in cultured primary human trophoblast cells, suggesting that OA may regulate turnover of placental lipids (106). PLIN2 is essential for trophoblast lipid accumulation in lipid droplets, which protects trophoblast cells from apoptosis during hypoxia (107). The protein expression of placental CGI-58 and PLIN2 was reported to be increased in obese mothers at term (106,107). Additionally, oxidized LDL inhibits trophoblast invasion (108) through oxysterol activation of LXR (109). Palmitic acid (16:0, PA), a saturated ‘lipotoxic’ fatty acid (110), stimulated IL-6, IL-8, PLIN2, and TLR expression and increased release of IL-8 in culture media in primary human trophoblast cells while OA did not have this effect (105,110,111). In general agreement with these findings, PA and TNF-α increased the expression of proinflammatory cytokines (IL-6, TNF-α, and IL-8) through JNK/EGR-1 signaling in human trophoblast cell lines, and placental JNK/EGR1 protein expression is elevated in maternal obesity (112).

Placental Omics in Maternal Obesity

The number of studies reporting placental ‘omics’ signatures in obese women is limited (Table 1), however two common themes emerge from these studies: placental transcripts, proteins and metabolites associated with lipid metabolism and inflammation/immune responses are differentially expressed in placentas exposed to maternal obesity.

Lipid metabolism is an enriched pathway common to multiple placental ‘omics’ studies in maternal obesity. The transcriptome of term placenta from obese women compared to placenta from normal BMI women revealed differential expression of genes uniquely

associated with lipid metabolism including decreased *APOE, DKK1* (113), *ANGPTL4* (114), and *NRIP1* (115) and increased lipid droplet-associated protein *CIDEA* (116), consistent with functional studies indicating increased TG content in cultured trophoblasts from obese women (117). Maternal obesity has also been associated with decreased placental expression of genes involved in retinoic acid (Vitamin A) transport and metabolism (*GPC4*, *ALDH1A1*, *ALDH1A2*, *CRABP2, RBP1*, *RBP4*, *SDC4*, and *PTGES)* (118), which in placenta are likely to be important for binding of maternal chylomicrons and lipoproteins (119). Reduced placental mTOR gene expression and up-regulation of the genes encoding proteins involved in oxidative stress and mitochondrial function, such as increased sirtuin 1 (SIRT1) and uncoupling protein 2 (UCP2), have been reported in maternal obesity (120). Moreover, placental liver X receptor (LXR) signaling pathway was enriched in placental transcripts from obese mothers, consistent with higher plasma levels of palmitic and oleic acid in the same cohort (121). LXR and the ATP-binding-cassette-transporter-A1 (ABCA1) have been proposed to transport maternal cholesterol at the MVM surface of the syncytiotrophoblast (122) and physiological studies have shown that LXR agonists increase cholesterol transport in trophoblast cells (123). Perturbations in placental lipid metabolism induced by maternal obesity are further supported by proteomic and metabolomic studies. In a recent report, the placental proteomic signature was consistent with increased lipid synthesis and energy production and altered antioxidant capacity in placenta from normoglycemic, obese women compared to normal weight mothers (124). These findings, in concert with data demonstrating higher lipid content and evidence of decreased antioxidant capacity in cultured trophoblasts from obese women, are in general agreement with the proposal that maternal obesity is associated with placental lipotoxicity (112,125).

Enrichment of inflammation and immune response pathways is also a common finding in the placenta in maternal obesity, consistent with the concept that maternal obesity is associated with mild placental inflammation (48,121,126). Placental cytokine-receptor signaling was consistently found to be enriched across multiple placental omics studies (121,125,127). Recent next-generation sequencing studies have demonstrated decreased mRNA expression of *LEP*, *ADIPOR1*, *IGFBP1*, *CCK*, *CRH*, *IL1R1*, *IL1R2* and accessory proteins *IL1RAP* and *IL1RAPL2* in maternal obesity as compared to normal weight women at term (121,125).

Untargeted approaches have been used to define a placental methylome (128,129) and recently it was shown that obesity influences DNA methylation patterns in the human placenta (130). Obese women had the highest levels of placental global methylation as compared to normal pregnancy and pregnancies complicated by GDM or preeclampsia (131). Placental transcripts that encode key proteins central to placental growth and metabolism, such as PPARα, IGF-2, and sirtuins, have also been shown to be differentially methylated in maternal obesity (128,130,132).

These studies provide a compelling resource of discovery data, identifying novel placental genes and signaling pathways that are influenced by maternal obesity and therefore may play a role in mediating changes in placental function Recently, approaches to integrate different modalities of ‘omics’ data have been employed. For example, integrative analysis

of the transcriptome and metabolome in the BeWo trophoblast cell line in response to high glucose, reflecting one isolated aspect of the obesogenic environment, demonstrated changes fatty acid and phospholipid metabolism (133,134). However, more targeted and mechanistic studies are required to confirm cause-and-effect relationships (135). The heterogeneity of placental tissue precludes assigning ‘omics’ signatures to specific cell types in studies using placental tissue and difficulties to isolate intact syncytium from human placenta has limited the interrogation of the syncytiotrophoblast transcriptome, proteome and metabolome. However, emerging single cell sequencing approaches developed to study the transcriptome of the normal trophoblast (136–140) will allow cell specific placental ‘omics’ approaches to be used in relation to maternal obesity and other pregnancy complications in the near future. Future use of approaches that employ barcoding strategies for single cell sequencing (MATQ-seq) as well as more functional ‘omics’ integrations such as chromatin immunoprecipitation sequencing in concert with selective isolation of chromatin-associated proteins (ChIP-SICAP; (141,142)) represent powerful tools to further explore placental ‘omics’ in maternal obesity.

Placental Inflammation

As discussed above, multiple reports indicate higher circulating levels of lipids, leptin, TNF-α, IL-1β, IL-6, IL-8 and reduced levels of adiponectin in obese women as compared to normal BMI pregnant women. The question to what extent there is placental inflammation in maternal obesity has been studied in some detail. At the RNA level, several studies have found that maternal obesity is associated with higher placental expression of TNFα, IL-1β, IL-8, MCP-1, and cytokine receptors such as CXCR2 at term (100,143–145). Placental TNF-α levels were reported to be elevated in female, but not male, placentas in maternal obesity, suggesting fetal sex differences in the placental inflammatory response to obesity (146). Moreover, maternal obesity is associated with the activation of distinct intracellular placental inflammatory pathways, including signal transducer activated transcription factor 3 (STAT3) and the stress/mitogen activated protein kinases (MAPK) p38 (68,147,148). The number, identity, and activity of immune cells within the placenta are likely to influence the degree of placental inflammation when exposed to maternal obesity. However, available information in this area remains limited. Challier and co-workers demonstrated increased number of CD14+ and CD68+ macrophages in the placenta in maternal obesity as compared to normal BMI women (10). Yet Roberts et al. reported a different placental immune response to maternal obesity, characterized by increased neutrophils and no change in CD14+ and CD68+ macrophages (143). Although placental inflammation in maternal obesity has been suggested to alter placental functions such fatty acid and amino acid transport, metabolism and insulin resistance (100,144,145), the molecular mechanisms linking inflammatory mediators to placental dysfunction in maternal obesity have been described for only a handful of inflammatory mediators (68,99,100,149) and those mediators were studied in isolation when a combination approach may be more physiological.

Placental Metabolism and Mitochondrial Function

As most other tissues, the human placenta relies on glycolysis and oxidative phosphorylation for the production of ATP (150), however the precise contribution to the overall energy

needs of the two sources of ATP remains to be clearly established. Elevated circulating concentrations of glucose and lipids in maternal obesity likely affect not only placental uptake but also its metabolism. Glucose has long been of interest for studies aimed at understanding fetal and placental growth. Under low oxygen conditions placental metabolism does not shift to anaerobic glycolysis (151) and hypoxia stimulates lipid accumulation in trophoblasts (152). The relatively high density of mitochondria and the presence of specialized long chain fatty acid uptake transporters (153,154) in human trophoblasts has led to the proposal that placental metabolism is highly oxidative and 'prefers' oxidative metabolism to glycolysis (155). Mele and colleagues reported that maternal obesity is associated with decreased placental ATP generation by oxidative phosphorylation without concomitant up-regulation of glycolysis (156). These findings were interpreted to indicate impaired placental mitochondrial function in maternal obesity (156). However, an alternative explanation might be a homeostatic down-regulation of mitochondrial function due to increased glucose availability *in vivo*, and therefore increased glycolytic glucose flux when the mother is obese and glucose levels are elevated.

β-oxidation is a key energy source for placental metabolism and circulating TGs, the source of placental lipids, are typically increased in maternal obesity (50). Placental β-oxidation, as measured using radiolabeled palmitate was found to be decreased and esterification and storage of lipids were increased in maternal obesity (117). However, when β-oxidation was prevented through chemical inhibition of long chain fatty acid carrier CPT-1, the rate limiting enzyme for fatty acids entry into the mitochondria, non-mitochondrial fatty acid oxidation was greater in placenta from obese compared to normal BMI women (117). Given that placental peroxisomal activity was enhanced in maternal obesity as compared to normal BMI women, the authors concluded that ~10% of trophoblast fatty acid oxidation was non-mitochondrial in maternal obesity, which may exacerbate ROS generation (117). Based on these considerations, it has been proposed that an oversupply of lipids to the placenta exceeds the placental mitochondrial capacity for β-oxidation, resulting in elevated intracellular placental lipid levels, increased lipid storage and promotion of fatty acid transfer to the fetus (106,117,125). Whether or not the infants of obese mothers are hyperlipidemic at birth has not been resolved, with some studies reporting no correlation between maternal BMI and cord or neonatal lipid profile (51,157,158) with other reports showing maternal BMI influenced neonatal TG levels (159).

In addition to glucose and fatty acids, emerging evidence suggest that glutamine, which enters the TCA cycle as α-ketoglutarate, is a major substrate for baseline oxidative phosphorylation in trophoblast cells from normal healthy pregnancy (160). Male, but not female, cultured primary human trophoblast cells isolated from placentas of obese mothers displayed increased preference for fatty acid and glucose at baseline but this preference was accompanied by a decrease in the ability to switch between glucose, fatty acid, and glutamine when oxidation demands increased (160). This apparent plasticity of placental mitochondria, together with differences in experimental buffers and culture conditions (161), *in vitro* oxidative stress or cell death, differentiation status (155,162), and delivery (labor) method (163,164), as well as the possibility that prolonged cell culture activates anaerobic glycolysis (165), are all contributing factors to the considerable variability in published basal mitochondrial respiration rates in human placental studies (163,166). These considerations

complicate interpretation of recent reports on the effect of maternal obesity on placental mitochondria and additional studies in this area are warranted.

Placental mitochondrial density increases across normal gestation (163). Mitochondrial biogenesis is regulated by a multitude of factors, including growth factor and mTOR signaling. For example, inhibition of mTORC1 signaling reduces mitochondrial biogenesis and decreases oxidative phosphorylation in cultured primary human trophoblast (167). Likewise, epidermal growth factor (EGF) is implicated in regulating mitochondrial density in placentas exposed to maternal obesity (155). Maternal obesity has been shown to reduce mitochondrial density in placenta or isolated trophoblasts (117,168). However, Mando and colleagues reported that maternal obesity, but not GDM, was associated with increased mitochondrial DNA as well as normal mitochondrial morphology in syncytiotrophoblast from obese women (169). Recently, mitochondrial density was linked to different trophoblast cell types in human pregnancies (155). Specifically, chemical prevention of primary human trophoblast syncytialization *in vitro* revealed that cytotrophoblasts have a higher mitochondrial density, rely more on oxidative phosphorylation and have a preference for fatty acids as energy substrate as compared to syncytialized cultured trophoblasts (155). These data suggest that cytotrophoblasts may play a more important role than previously recognized and that increased lipid availability may contribute to cytotrophoblast hyperplasia. The mechanistic links between maternal obesity and changes in placental mitochondrial function remain to be established.

Placental Reactive Oxygen Species and Oxidative Stress in Maternal Obesity

The levels of reactive oxygen species (ROS) typically refer to the abundance of chemically reactive molecules containing oxygen, including peroxides, superoxide and hydroxyl radical. Higher levels of ROS may or may not be associated with oxidative stress (i.e., higher levels of ROS that cause some type of damage) depending on to what extent antioxidant defense mechanisms are activated. In non-pregnant individuals, obesity is associated with higher levels of reactive oxygen species (ROS) and oxidative stress (170). ROS species relevant for obesity include endogenous free radicals (O_2^- and HO), hydrogen peroxide, and ozone originating from mitochondria but also peroxisomal degradation of branched chain fatty acids, NADPH oxidases, purine degradation, and eicosanoid metabolism. Maternal obesity has been associated with increased maternal ROS including higher levels of maternal malondialdehyde, carbonyl proteins, nitric oxide and superoxide anion with lower glutathione concentrations and superoxide dismutase (SOD) activity (168,171). Moreover, ROS production (156), glutathione concentrations and SOD activity (171) in the placenta is reported to be increased in maternal obesity, which may impair mitochondrial function and explain lower ATP production (156). This is supported by studies in other tissues where prolonged ROS exposure impairs mitochondrial function through mechanisms such as reduced ability to replicate mitochondrial DNA (172) and activation of ROS-dependent cell death mechanisms (173). In situations of nutrient excess, such as maternal obesity, mechanisms to uncouple substrate metabolism to ATP synthesis, including increased expression of uncoupling proteins (UCP2) and antioxidants, normally

limit ROS accumulation. In general agreement with this concept, placental activity of superoxide dismutase and catalase is increased in maternal obesity compared to normal BMI mothers (171). Moreover, a recent study linked decreased placental expression of the antioxidant glutathione peroxidase 4 in maternal obesity to markers of oxidative stress in the newborn (174), suggesting that placental oxidative stress may be transmitted to the fetus with possible negative effects on fetal development.

Fatty acids reflect an additional source of placental ROS accumulation through processes in the mitochondria (during anaplerosis) and in the cytoplasm through the action of NADPH oxidase (175). The high circulating maternal lipid levels and higher placental ROS with dysfunctional mitochondria in maternal obesity likely results in the production of oxidized lipid products, including lipid peroxides (176), oxidized lipoproteins (177) and oxysterols, that may adversely impact trophoblast function. Because oxysterols are ligands for LXR, which increases expression of genes involved cholesterol and lipid metabolism, these changes may influence placental lipid transport and/or metabolism. Furthermore, the placenta produces nitric oxide (NO) that can form peroxynitrite, a pro-oxidant that causes excessive protein nitration (nitrative stress). Placental nitrative stress, measured by nitrotyrosine protein modifications, is increased in obese compared to normal weight women (178) and represents a potential link between ROS and redox dysfunction and intracellular signaling pathways (179).

Placental signaling

Receptors for a range of hormones and growth factors, including receptors for adiponectin, insulin (76), leptin (180), and IGF-1 (71), are highly expressed in the maternal facing MVM of the syncytiotrophoblast, consistent with maternal regulation of placental function. In maternal obesity, the effects of changes in maternal levels of hormones and growth factors and increased nutrient levels are believed to modulate intracellular signaling cascades that converge on key nutrient sensing pathways in the placenta. The extent to which the activity of placental growth-promoting signaling pathways are affected by maternal obesity seems to be dependent the degree of excess maternal body fat mass and whether fetal growth is increased, with more pronounced changes found in women with the high BMI giving birth to LGA babies (120,144,181,182).

The expression and/or phosphorylation of the placental insulin/IGF signaling machinery, including down-stream targets IRS-1 and Akt are increased in obese women delivering LGA babies (144). Activation of placental insulin/IGF signaling in maternal obesity is likely to be caused, in part, by the low maternal levels of circulating adiponectin because adiponectin inhibits trophoblast insulin signaling at the level of IRS-1, mediated by activation of PPARα and ceramide synthesis (84,85)(Figure 2). Furthermore, the activity of placental AMPK, a primary energy sensor that is phosphorylated when ATP levels are low, was reported to be markedly decreased in association with maternal obesity and fetal overgrowth (144) indicating ample availability of energy substrates in the placenta of obese mothers in which fetal growth acceleration occurs. mTOR signaling integrates a large number of metabolic factors, including hormone and growth factor signaling, such as insulin, IGF-1 and EGF, ATP/energy levels, amino acids, glucose, and fatty acids levels, in order to coordinate

cellular metabolism, growth, and proliferation (183) in response to the availability of substrates. There is now compelling evidence that mTOR serves as a critical node in coordinating placental function in response to maternal factors to match fetal growth to the ability of the mother to provide adequate nutritional support (184). AMPK inhibits mTOR Complex 1 and decreased AMPK signaling in combination with activation of insulin/IGF signaling and a high availability of nutrients may contribute to an activation of placental mTOR signaling in maternal obesity (144). Because mTOR signaling is a positive regulator of an array of key placental functions, including amino acid transport (185,186), folate transport (187) and mitochondrial biogenesis (167), it has been proposed that activation of placental mTOR signaling may contribute to enhanced fetal nutrient delivery and fetal overgrowth (Figure 2), which occurs more commonly in obese women (144).

Placental nuclear receptors, such as PPARγ and RXR, are also influenced by maternal obesity. For example, placental PPARγ RNA and protein levels are increased in maternal obesity (117), which may modulate placental development and function given the well-established effects of PPARγ on trophoblast invasion, fatty acid metabolism, and inflammatory responses (188). Both activation of PPARγ and RXR increased fatty acid uptake in primary human trophoblast cells through increased expression fatty acid transport protein 4 (FATP4 (189)).

Nutrient Transport

Placental nutrient transport capacity is one key determinant of fetal growth and there is evidence from human placenta of increased expression/activity of transporters for glucose, amino acids and lipids in pregnancies complicated by maternal obesity, in particular in cases of fetal overgrowth.

Glucose

Glucose is a major metabolic substrate for the placenta and the fetus and the majority of glucose taken up from the mother is transported to the fetus (190). Placental glucose uptake from the maternal circulation is believed to be mediated predominantly by glucose transporter 1 (GLUT-1) expressed in the MVM. Transport to the fetal circulation across the BM, which is traditionally considered the rate-limiting step in maternal-fetal glucose transfer, is also accomplished by GLUT-1. While glucose moves across the placenta by facilitated diffusion and higher postprandial maternal glucose levels in maternal obesity result in increased fetal glucose to support accelerated fetal growth, some evidence suggests that placental glucose transport capacity, as reflected by an increased expression of glucose transporters in the placental barrier, is increased in maternal obesity. For example, BM GLUT-1 expression correlated with birth weight in obese mothers without diabetes (191), suggesting the capacity of the placenta to transfer glucose modulates fetal growth in these pregnancies. Moreover, GLUT1 expression was increased in the BM in primary human trophoblast cells isolated from pregnancies complicated with maternal obesity (191,192). This increased placental glucose transport capacity when exposed to maternal obesity may contribute to increased glucose delivery to the fetus and promote fetal overgrowth even if the mother is euglycemic.

Amino Acids

Placental amino acid transporter systems A and L have been studied extensively. The System A transporter, predominantly expressed in the MVM, mediates the uptake of non-essential neutral amino acids from maternal blood in the intervillous space into the cytosol of the syncytiotrophoblast, energized by the inwardly directly sodium gradient (20,193,194). As a result, the syncytium has high intracellular concentrations of amino acids. System L exchanges essential amino acids such as leucine in the maternal blood for non-essential amino acids, which are accumulated in the cytoplasm by System A. In this way the two transporters work in concert to increase the intracellular concentrations of both essential and non-essential amino acids, which then diffuse across the BM to the fetal circulation. System A activity but not System L was positively correlated with birth weight in a cohort of normal and obese women (144). Unlike system A amino acid transport, placental transport of taurine, a β-amino acid, was lower in obese compared to normal BMI women (195). The inverse relationship between taurine transporter and maternal BMI, suggests obesity impacts placenta taurine consumption and ultimately fetal efflux (195). Placental mTOR signaling is activated in obese women giving birth to LGA babies (144), likely due to a combination of multiple factors, including elevated maternal insulin and leptin as well as low adiponectin levels and elevated levels of nutrients. Activation of mTORC1 and mTORC2 independently activate trophoblast System A and System L amino acid transporter activity by modulation of plasma membrane trafficking of two key transporter isoforms, SNAT2 and LAT1 (185,196). Whereas mTORC1 modulates SNAT2 and LAT1 trafficking by Nedd4-2-regulated ubiquitination (197), mTORC2 regulates amino acid transporters trafficking mediated by Cdc42 and Rac1 and effects on the actin skeleton ((196); Figure 2)). Therefore, as with glucose, the increased capacity to transport amino acids may promote increased fetal growth *in utero* in some pregnancies complicated by maternal obesity.

Lipids

Maternal circulating TGs and NEFAs are elevated in pregnancy, providing the necessary fatty acids for transport to the fetus. Placental uptake of NEFA occurs primarily via several isoforms of fatty acid transport proteins, FAT/CD36 and specific fatty acid binding proteins localized in the MVM (198). Maternal obesity may have distinct effects on the expression of different fatty acid transporters in the placenta. High BMI women had decreased mRNA expression of FATP1 and FATP4 but increased protein expression of FATP6 and FAT/CD36 in placenta compared to normal BMI women (199). Lager and colleagues, using isolated syncytiotrophoblast plasma membranes, reported higher FATP2 and FATP4 in BM compared to MVM and FATP2 protein abundance in the BM correlated to maternal BMI, suggesting an increase capacity to transfer NEFAs to the fetus (200). In addition, maternal obesity is associated with increased placental lipid accumulation (117) but others have reported lower saturated fatty acid content (199) and impaired ability of the placenta to deliver long chain polyunsaturated fatty acid (LCPUFA) to the fetus (124). There is limited knowledge on what factors regulate expression of placental fatty acid transporters, re-esterification pathways and β-oxidation in the placenta of obese mothers. Szabo and co-workers have proposed that lipid transfer to the fetus is increased in pregnancies complicated by maternal obesity, resulting in greater fetal adipogenesis (201). However, the effect of maternal obesity on placental lipid

transport and storage remains to be fully established and represents a high priority area for future research.

Effect of Clinical Interventions on Placental Function in Maternal Obesity

Exercise and lifestyle interventions in prospective trials have been explored in maternal obesity as a way to decrease adverse maternal (such as gestational weight gain, hypertensive disorders, GDM and dysfunctional labor) and infant outcomes (including fetal overgrowth). Although these interventions have been shown to reduce maternal weight gain in pregnancy, no effect on birth weight or incidence of fetal overgrowth have been demonstrated (202,203). Moreover, exercise and lifestyle interventions may have a positive effects on infant body composition and maternal health (9,204). The impact of exercise and lifestyle interventions on placental function in obese women remain largely unknown, although effects on placental development and function have been proposed to underlie ‘paradoxical’ findings of increased fetal weights following an exercise intervention (205).

Omega 3 polyunsaturated fatty acids (n-3 LCPUFAs) have been proposed to be a safe anti-inflammatory mediator to improve outcomes in maternal obesity (206). A recent meta-analysis indicated lower risk for LGA with n-3 LCPUFAs supplementation (207). Moreover, Lager and coworkers demonstrated improved placental function following 800 mg per day DHA supplementation in the second half of pregnancy in obese women. They found that higher levels of placental DHA were associated with decreased amino acid transporter expression and reduced inflammatory markers but also an increase in placental fatty acid transporter expression (208). A follow-up study of a small number of infants from the trial indicated reduced adiposity in the children of supplemented mothers at 2 and 4 years of age, an effect that was not due to differences in duration or exclusivity of breast feeding (209).

Given the relatively limited success of traditional dietary and lifestyle interventions in alleviating adverse pregnancy outcomes in obese women, there is a significant interest in exploring more targeted intervention strategies. Anti-inflammatory agents such as resveratrol have been explored in placental explants treated with LPS or poly(I:C). Resveratrol reduced the mRNA expression of TNF-α, IL-1β, IL-6, IL8 as well as culture media concentrations of IL-6, IL-8, and MCP-1 (210), increased AMPK phosphorylation and decreased uptake of glucose as well as DHA and arachidonic acid (AA) but decreased β-oxidation and did not affect rates of FA esterification (211). However, a recent study suggests caution because administration of resveratrol in pregnant nonhuman primates was associated with negative effects on the fetus (212). In a recent study in isolated primary trophoblasts from normal BMI and obese women, melatonin effectively reduced expression of some antioxidants and increased total respiratory capacity of trophoblasts from obese women but not from normal BMI mothers (213).

Integrated Model

Maternal obesity increases the risk of fetal overgrowth, which is associated with poor maternal outcomes including emergency Caesarean section, obstetrical trauma, postpartum hemorrhage and diabetes as well as risks for the infants, such as shoulder dystocia, brachial

plexus injury, skeletal injuries, meconium aspiration, perinatal asphyxia, hypoglycemia, and fetal death (31,214). Infants of obese mothers also tend to have increased adiposity (215,216) and/or insulin resistance at birth (61). A series of recent alarming reports link fetal exposure to the adverse metabolic environment of the obese mother with later development of the metabolic syndrome and cardiovascular disease, in particular if the infants were large at birth (12–18,47,217–228). Collectively, these studies suggest that infants of obese mothers that are large and/or have increased adiposity at birth are particularly susceptible to poor short- and long-term outcomes. Therefore, preventing fetal overgrowth and/or increased fat mass in infants of obese mothers is an important objective in the development of novel intervention strategies.

Available literature strongly suggests that the mechanistic link between maternal obesity, fetal overgrowth/increased infant adiposity and programming of adult disease involves specific changes in the placenta (Figure 3). High insulin, leptin, IGF-1 and nutrient levels and low adiponectin in the maternal circulation are key examples of factors that converge to activate placental mTOR signalling, a positive regulator of an array of key placental functions, including amino acid transport (185,186), folate transport (187) and mitochondrial biogenesis (167). These changes are proposed to promote nutrient delivery to the fetus, increased fetal growth and/or adiposity, which are strongly linked to the development of metabolic and cardiovascular disease in childhood and adult life (Figure 3). We recently reported that normalization of maternal circulating adiponectin in a mouse model of obesity prevented the activation of placental mTOR signaling and nutrient transport, fetal overgrowth and programming of metabolic and cardiovascular disease in the offspring (58,229,230), supporting the concept that low maternal adiponectin, activation of placental mTOR signaling and nutrient transport are not only important in accelerating fetal growth but may also be critical for the programming of adult disease in offspring of obese mothers. Given that the majority of obese women give birth to normal sized infants (11,219,231,232), studies of these pregnancies are essential. Changes in placental function in these pregnancies include activation of inflammatory signalling pathways (10,68,112,143), signs of oxidative stress (171,174,178), decreased oxidative phosphorylation (145,156,168,169), and possibly lipid accumulation (49,106,117,125,199,217), however whether these alterations are linked to poor short and long-term infant outcomes remains to be fully established.

Conclusion and Future perspectives

Given the rapidly increased prevalence of maternal obesity in pregnancy worldwide, the poor long- and short-term outcomes in infants of obese mothers represent a major public health problem in the 21st century. A recent meta-analysis shows that dietary and lifestyle interventions in overweight and obese women have only limited beneficial effects on birth weight and other key obstetrical outcomes (233). Furthermore, lifestyle changes and anti-obesity drugs in children and adults remain largely unsuccessful, highlighting the urgent need to better understand the molecular underpinnings linking maternal obesity to poor short- and long-term outcomes in order to allow for the development of specific interventions during pregnancy to prevent metabolic programming. Although an individuals' life-long health trajectory may be determined by the first 1000 days of life (i.e., from conception up to two years of postnatal life) (234), fetal life appears to be of particular

importance for the programming effect of maternal obesity. Thus, *in utero* intervention is an attractive and likely efficient approach to prevent childhood obesity and metabolic syndrome in the next generation.

A large body of epidemiological data suggests that altered placental structure and function increases the risk of developing diseases such as obesity, diabetes, cardiovascular disease, and cancer in adult life (235–242). Emerging evidence in mice demonstrates that the placenta directly influences fetal brain development and that changes in placental function mediate the link between maternal obstetrical complications and adverse neurodevelopmental outcomes (243–247). Thus, the placenta determines life-long metabolic and mental health and understanding the functions of the placenta may hold the key to unravelling the molecular pathways underpinning developmental programming in response to maternal obesity. Well-designed mechanistic experiments in relevant animal models guided by observational data obtained in pregnant women will be instrumental in this area. Of particular interest is to determine the molecular pathways causing placental oxidative stress, altered mitochondrial function and lipid handling and low-grade inflammation in maternal obesity and how these placental changes specifically leads to poor short- and long-term outcomes. This will provide a critical foundation for developing interventions that specifically target placental function in women who enter pregnancy obese. We speculate that activation of placental adiponectin receptors by maternal adiponectin supplementation, interventions enhancing endogenous adiponectin secretion or administration of adiponectin receptor agonists represent a promising future clinical intervention in pregnancies complicated by obesity in which maternal adiponectin levels are low.

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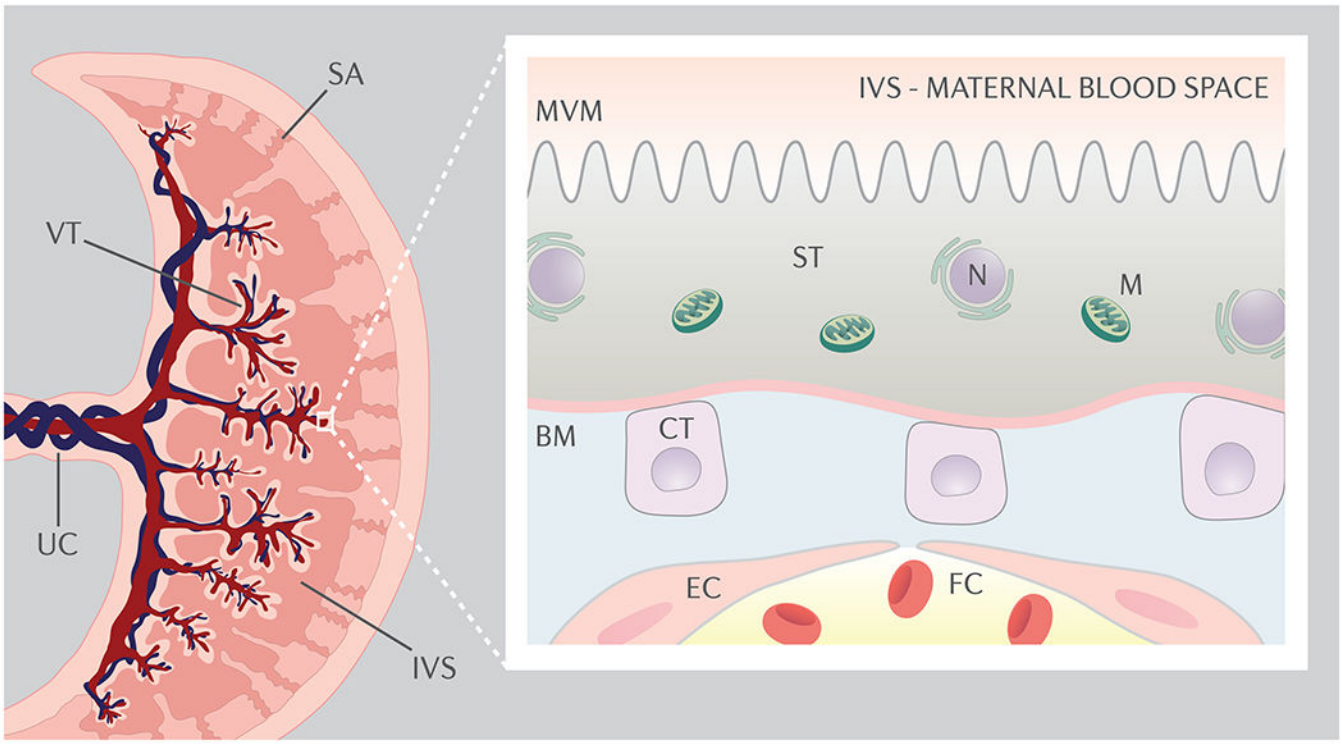

Figure 1. The human placental barrier at term.

The functional unit of the human placenta is the trophoblast villous tree (VT), containing fetal blood vessels and covered by the syncytiotrophoblast (ST), the multinuclear transporting and hormone producing epithelium of the human placenta, which is generated from mononuclear cytotrophoblast cells (CT). The syncytiotrophoblast is directly exposed to maternal blood entering the intervillous space (IVS) from the spiral arteries (SA). At term, the syncytiotrophoblast and the fetal capillary (FC) endothelial cells (EC) are the only largely continuous cell layers between maternal and fetal blood. The syncytiotrophoblast represents the primary barrier for movement of most solutes from the maternal to the fetal circulations. Specifically, transfer across the two polarized plasma membranes of the syncytiotrophoblast, the apical or microvillous plasma membrane (MVM) directed toward maternal blood in the intervillous space and the basal plasma membrane (BM) facing the fetal capillaries constitute the limiting steps for net flux from maternal to fetal circulations. UC, umbilical cord; N, nucleus, M; mitochondrion.

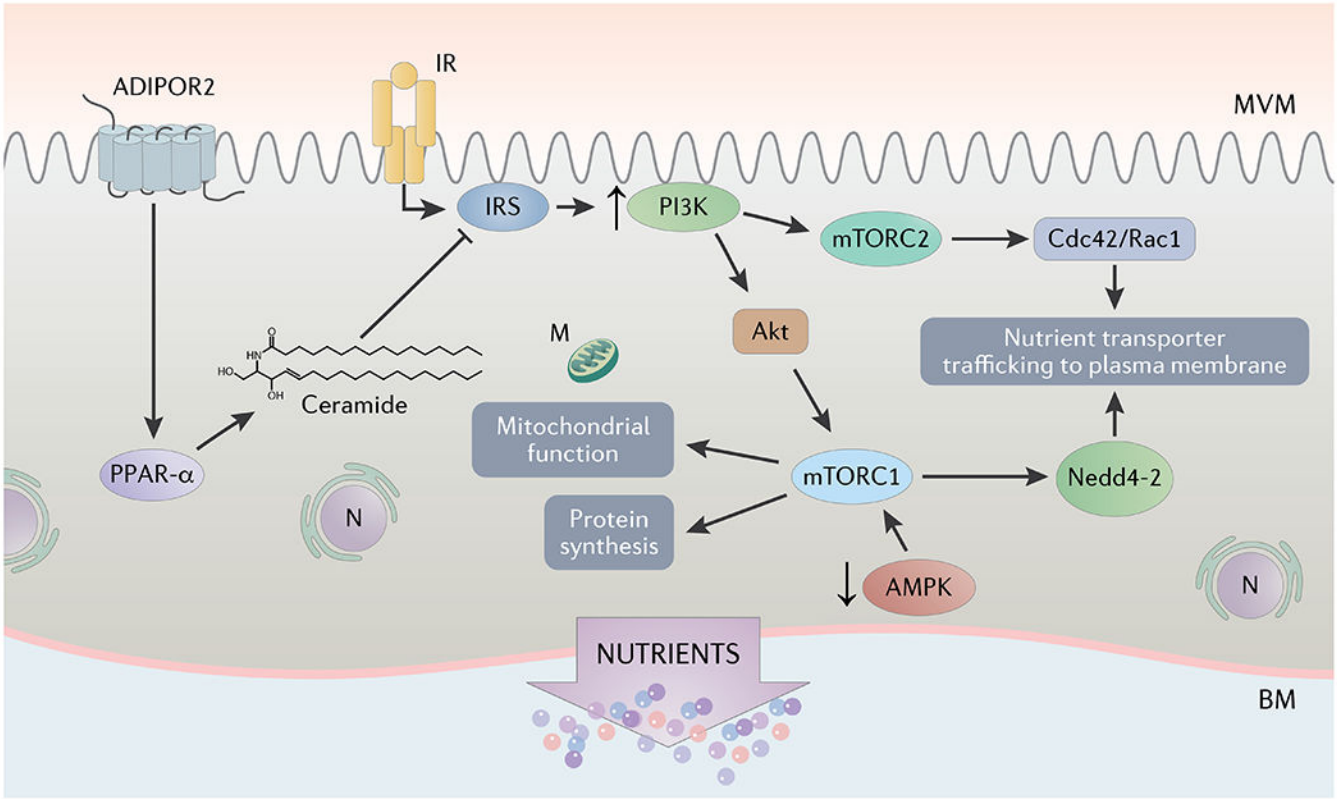

Figure 2. Trophoblast signaling in obese women delivering large for gestational age babies.
Placental insulin/IGF signaling is activated in obese women delivering large babies, likely due to maternal hyperinsulinemia with maintained placental insulin responsiveness. Moreover, adiponectin inhibits trophoblast insulin signaling at the level of IRS-1, mediated by activation of PPARα and ceramide synthesis. Thus, the low maternal levels of circulating adiponectin in maternal obesity are likely to contribute to the activation of placental insulin signaling. AMPK inhibits mTOR Complex 1 (mTORC1) and decreased AMPK signaling in combination with activation of insulin/IGF signaling and a high availability of nutrients may contribute to an activation of trophoblast mTOR signaling in maternal obesity. Activation of mTORC1 and mTOR complex 2 (mTORC2) independently stimulate trophoblast amino acid transport mediated by distinct mechanisms. Whereas mTORC1 influences amino acid transport by Nedd4-2 mediated ubiquitination, mTORC2 promotes trophoblast amino acid transport by activating Cdc 42/Rac 1. Because mTOR signaling is a positive regulator of an array of key placental functions, including amino acid and folate transport and mitochondrial biogenesis, it has been proposed that activation of placental mTOR signaling may promote increased nutrient delivery to the fetus, contributing to fetal overgrowth. ADIPOR2, adiponectin receptor 2; IR, insulin receptor; PPAR-α, peroxisome proliferator-activated receptor alpha; IRS, insulin receptor substrate; mTORC1, mechanistic target of rapamycin complex 1; mTORC2, mechanistic target of rapamycin complex 2; Cdc42, cell division control protein 42; Rac1, Ras-related C3 botulinum toxin substrate 1; Nedd4-2, neuronal precursor cell-expressed, developmentally downregulated gene 4 isoform 2; AMPK, AMP-activated protein kinase; N, nucleus, M; mitochondrion.

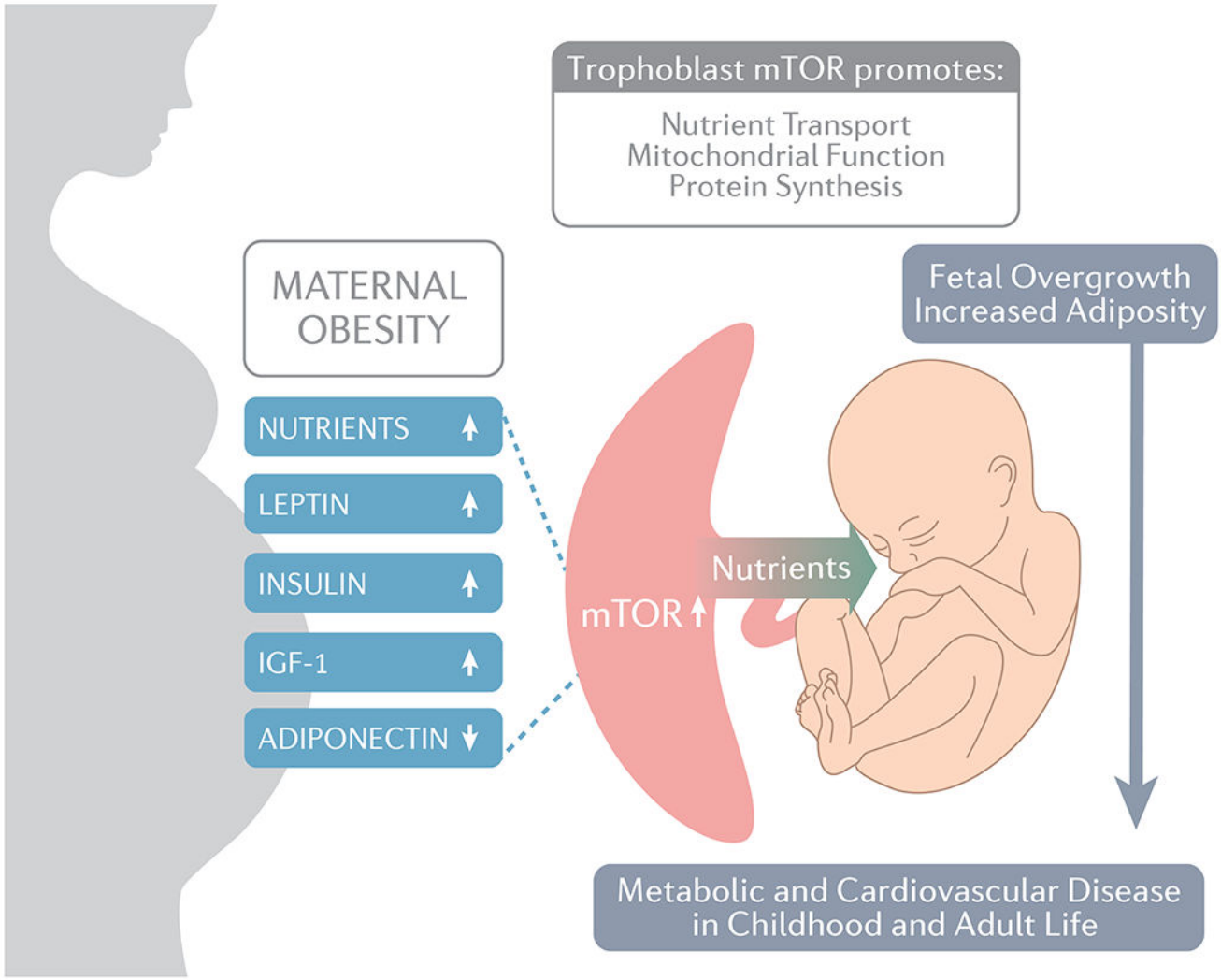

Figure 3. Proposed model of mechanistic links between maternal obesity, fetal overgrowth/ increased infant adiposity and fetal programming of adult disease.

We propose that the mechanistic link between maternal obesity, fetal overgrowth/increased infant adiposity and programming of adult disease involves specific changes in the placenta from increased mTOR signaling. High insulin, leptin, IGF-1 and nutrient levels and low adiponectin in the maternal circulation are key examples of factors that converge to activate placental mTOR signalling, a positive regulator of an array of key placental functions, including amino acid transport and mitochondrial biogenesis. Some of the proposed involved signaling mechanisms are depicted in more detail in Figure 2. These changes are proposed to promote the delivery of nutrients (which may include glucose, amino acids and lipids) to the fetus, increased fetal growth and/or adiposity, which are strongly linked to the development of metabolic and cardiovascular disease in childhood and adult life. IGF-1, insulin-like growth factor 1; mTOR, mechanistic target of rapamycin.

Table 1:

Human placental omics studies in maternal obesity.

Clinical Characteristics of Study Subjects	Tissue Type	Gestational Age/ Delivery Mode	Omics Approach
Proteins and Metabolites			
Normal BMI	Placental tissue	Term; C/S	Proteome (253)
Obese (Normoglycemic) and normal BMI	Placental biopsies	Term; C/S	Metabolome (GC-MS) (136)
mRNA and miRNA			
Obese, overweight, and normal BMI	Placental tissue	Term	Microarray (254)
Obese and normal BMI	Placental tissue	Term	Microarray (133)
Obese and normal BMI	Isolated primary trophoblasts	7-12 weeks; elective termination	Microarray (138)
GDM, obese, and normal BMI	Isolated trophoblast	Term; C/S	Laser microdissection prior to microarray (139)
Obese and normal BMI	Placental tissue	Term	RNAseq (137)
Obese and normal BMI	Placental tissue and placental microbiome	Term	RNAseq and 16S-seq (130)
Non-diabetic women delivering large for gestational age infants	Placental tissue	Term	lncRNA and mRNA Array (255)
DNA methylation			
Obese and normal BMI	Villus tissue	Term; C/S	Methylation MeDIP/hMeDIP (144)
Obese, GDM, pre-eclamptic, and normal BMI	Placental tissue	Term	Methylation (143)
Overweight/obese (BMI>25) and normal BMI	Placental tissue	Term	Methylation, Unpublished: GSE120062

Normal BMI defined as BMI<25. GDM, Gestational Diabetes; C/S Cesarean Section; GC-MS, Gas Chromatography-Mass Spectrometry; lncRNA, long non-coding RNAs; MeDIP/hMeDIP, Methy/ 5-hydroxymethylcytosine DNA Immunoprecipitation.