**Persistent Influence of Maternal Obesity on Offspring Health: Mechanisms from Animal Models
and Clinical Studies**

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ABSTRACT

The consequences of excessive maternal weight and adiposity at conception for the offspring are now well recognized. Maternal obesity increases the risk of overweight and obesity even in children born with appropriate-for-gestational age (AGA) birth weights. Studies in animal models have employed both caloric excess and manipulation of macronutrients (especially high-fat) to mimic hypercaloric intake present in obesity. Findings from these studies show transmission of susceptibility to obesity, metabolic dysfunction, alterations in glucose homeostasis, hepatic steatosis, skeletal muscle metabolism and neuroendocrine changes in the offspring. This review summarizes the essential literature in this area in both experimental and clinical domains and focuses on the translatable aspects of these experimental studies. Moreover this review highlights emerging mechanisms broadly explaining maternal obesity-associated developmental programming. The roles of early developmental alterations and placental adaptations are also reviewed. Increasing evidence also points to changes in the epigenome and other emerging mechanisms such as alterations in the microbiome that may contribute to persistent changes in the offspring. Finally, we examine potential interventions that have been employed in clinical cohorts.

Keywords: maternal obesity, development programming, epigenetics, metabolism

1. Introduction

The pivotal role of intrauterine experience in shaping the trajectory of health and disease susceptibility in later-life is now widely recognized and has permeated most disciplines of medicine. In the 1980s, Prof. David Barker and his colleagues proposed the ‘fetal origins of adult disease’ hypothesis in an attempt to explain the relationship between *in utero* growth and adult cardiovascular disease. Barker’s initial findings identified a correlation between maternal under-nutrition during gestation and increased offspring cardiovascular disease risk later in life. This concept has now burgeoned into what is now recognized broadly as the Developmental Origins of Health and Disease (DoHAD) paradigm to describe how environmental factors broadly during critical periods of development can influence offspring gene expression and phenotypic outcomes and modulate adult health. While many people in the world are faced with undernutrition, the increasing prevalence of overweight and obesity is a growing global health issue with persistent long-term consequences in terms of co-morbidities such as diabetes and metabolic disease. According to the 2013 Global Burden of Disease Study, 37% of men and 38% of women worldwide are overweight or obese (body mass index (BMI) of 25 kg/m² or greater), and approximately 2.1 billion people are overweight¹. In the United States, the prevalence of overweight and obesity is considerably greater, as 68.8% of adults have a BMI of 25 kg/m² or greater and 35.7% of US adults are considered obese. More alarming is the fact that over 60% of pregnancies in the United States are in women who are either overweight or obese at conception². Maternal obesity during pregnancy adversely affects the immediate health of both the mother and offspring^{3,4} and it is widely recognized that maternal obesity leads to developmental programming of excessive weight and adiposity in the offspring⁵. While there are many studies documenting that obesity-associated conditions such as excessive gestational weight gain and

gestational diabetes also have long-term effects on offspring health and development, this review will focus on the impact of maternal obesity on offspring health and development in both translational experimental and clinical domains and provide insights into emerging mechanisms of this cycle of obesity propagation (Figure 1).

Effects of maternal obesity on reproduction and fertility

Maternal obesity is associated with a number of adverse reproductive outcomes. Obese women have decreased rates of spontaneous pregnancy, longer time to conception, and are at higher risk of miscarriage, preeclampsia, gestational diabetes mellitus (GDM) and congenital birth defects compared to normal weight women. In addition, obese women experience poorer outcomes of fertility treatment and often require higher doses of ovulation-inducing agents. While obesity can affect endometrial receptivity, a study of over 45,000 assisted reproductive embryo transfers demonstrated that a higher BMI correlated with reduced likelihood of successful pregnancy when autologous oocytes were used, but not when oocytes from lean donors were used^{6,7}. These data suggest that oocyte quality is a critical factor in determining reproductive outcome⁸. Specifically, obesity is associated with decreased oocyte acid transport proteins, increased lipid content, and increased production of reactive oxygen species secondary to mitochondrial dysfunction and these disruptions in oocyte metabolism manifest as meiotic defects, organelle dysfunction (mitochondrial and ER) and epigenetic alterations that act in concert to diminish oocyte quality and reproductive potential⁹⁻¹². Obesity is also associated with changes in ovarian granulosa cells and the follicular fluid surrounding the oocyte. Granulosa cells from obese mice have increased rates of apoptosis and decreased mitochondrial function¹³, and obese women have increased follicular fluid triglyceride levels that presumably contribute to oocyte lipotoxicity and reduced fertilization rates¹⁴. Thus, perturbations in oocyte metabolism

might contribute to diminished reproductive potential in obese women. More importantly, animal studies demonstrate that exposure to maternal obesity increases inflammatory gene expression in the peri-implantation blastocyst (dpc 4.5)¹⁵.

Pregnancy-associated changes in maternal metabolism

There are many maternal physiological and anatomical adaptations to pregnancy that begin early after conception to accommodate the nutritional needs of the growing fetus. During pregnancy there is an increase in fluid retention, blood volume expansion, increase in heart rate, decrease in peripheral vascular resistance, changes in thyroid function/hormone production, increase in basal metabolic rate, and a number of other important adaptations. These maternal pregnancy-associated physiological changes include endocrine and metabolic adaptations, many of which are driven *via* placental-derived hormones. Placental factors including steroids and hormones mediate both maternal recognition of pregnancy and orchestrate adaptations necessary for a healthy pregnancy at the local and systemic levels. Late in gestation, maternal fuel utilization switches from carbohydrate to fat usage to ensure a continuous supply of glucose and amino acids to the growing fetus^{16,17}. Pregnancy is associated with increased insulin secretion¹⁸, partially *via* hypertrophy and hyperplasia of pancreatic β -islet cells. Early in pregnancy insulin sensitivity is increased, but starting in the 2nd trimester, women become increasingly insulin resistant as pregnancy progresses, due in part to the release of placental hormones including cortisol, prolactin, human placental lactogen, and progesterone. Increasing insulin resistance in the mother maintains nutrient flow to the growing fetus, whereas prolactin and placental lactogen counterbalance this resistance and prevent maternal hyperglycemia by driving expansion of the maternal population of insulin-producing beta cells. Downstream of prolactin signaling, serotonin synthesis within the β -cells is required for this expansion^{19,20}.

Mechanistically, several factors contribute to the development of insulin resistance in pregnancy; insulin is less able to phosphorylate the insulin receptor (IR) on skeletal muscle, adipose and skeletal muscle expression of IRS-1 is decreased and adipose and skeletal muscle expression of the regulatory p85 α subunit of PI3-K is increased²¹. Placental-derived TNF α and leptin seem to play important roles in modulating maternal skeletal muscle and hepatic insulin sensitivity. While fasting and postprandial insulin levels are increased in pregnancy, fasting glucose levels are lower due to increased plasma volume (dilution effect), increased tissue glycogen storage, increased peripheral glucose utilization, and increased fetal glucose consumption. Moreover, hepatic glucose production is increased to compensate for the increase in insulin secretion, but this compensation is incomplete and unable to sustain adequate glucose production. Hence, the net result of insulin resistance and hypoglycemia in late pregnancy is increased maternal lipolysis and increased circulating free fatty acids, which may in turn further contribute to insulin resistance in pregnancy. Early on in pregnancy there are measurable differences in insulin sensitivity in obese compared to lean women and though insulin sensitivity decreases as pregnancy progresses, obese pregnant women become more insulin resistant compared to normal weight pregnant women²².

Maternal adipose accretion, mostly in centrally-distributed subcutaneous fat, is a process that normally occurs in healthy pregnant women. In addition to the insulin resistance-associated increased lipolysis, other metabolic perturbations in maternal lipid metabolism occur during pregnancy. For example, pregnancy is associated with increased hepatic lipase activity, reduced lipoprotein lipase, and increased apolipoproteins, as well as a 2-4 fold increase in triglycerides, 25-50% increase cholesterol, increased LDL cholesterol and increased HDL cholesterol as pregnancy progresses²². Pregnancy is also associated with a number of changes in adipose tissue

and adipokine production. Though leptin levels increase in pregnancy, appetite and food intake continue to increase due to central leptin resistance²³. Conversely, levels of the insulin sensitizing adipokine, adiponectin, decrease in pregnancy and obesity during pregnancy is associated with hypo-adiponectinemia due to decreased adiponectin mRNA expression and increased methylation of the adipose tissue adiponectin gene. In normal weight women, early gestation (12-14 wk) is associated with net lipogenesis and late gestation (34-36 wk) is associated with net lipolysis. In contrast, in obese women, all stages of gestation are associated with net lipolysis, suggesting that the developing fetus of obese women is exposed to high levels of free fatty acids throughout all stages of *in utero* development.

2. Early life effects of maternal obesity in the neonate

There are many early life complications of maternal obesity for the neonate²⁴. Early pregnancy complications of maternal obesity include increased rates of spontaneous abortion (miscarriage), recurrent miscarriage, and congenital anomalies (neural tube defects, spina bifida, congenital heart disease, omphalocele). In late pregnancy, maternal obesity increases the risk of hypertensive disorders of pregnancy (gestational non-proteinuric hypertension and preeclampsia), gestational diabetes mellitus, preterm birth, and intrauterine fetal demise (still birth). Peripartum complications of maternal obesity include increased incidence of cesarean delivery, decreased vaginal birth after cesarean (VBAC) success, and operative morbidities (anesthesia complications, excessive blood loss, postpartum endometritis, wound infection and postpartum thrombophlebitis)²⁵. While it is still unknown why the rate of cesarean delivery is higher in obese pregnant women, it is possible that obese women experience dysfunctional labor since the rate of cervical dilation in both spontaneous²⁶ and induced labor²⁷ was inversely related to maternal BMI. Acute neonatal outcomes of *in utero* exposure to maternal obesity include

increased risk of fetal macrosomia (birth weight greater than 4500g), increased fetal adiposity, fetal insulin resistance, and shoulder dystocia^{25,28}.

3. Long-term effects of maternal obesity

The long-term effects of maternal obesity on offspring health and development have been studied in several animal models, namely mice, rats, sheep, and non-human primates, in addition to numerous cohort studies and epidemiological studies in human populations. One major concern with the experimental literature examining the long-term effects of maternal obesity is that the types and durations of diets used to induce maternal obesity are not standardized. For example, many of the rodent diet compositions vary widely in the percent of calories from fat (often 45-60% of calories from fat) and the sources of fat (lard, corn oil, etc) and thus fatty acid composition and cholesterol content also vary. Other nutritional factors such as sodium content, and fructose/sucrose content are variable and *in utero* exposures also likely effect offspring health and development. Williams *et al* has comprehensively reviewed the existing literature of mouse, rat and non-human primate models of *in utero* exposure to high fat diet²⁹. In addition, maternal obesity programs dysfunction in many ways, including but not limited to offspring metabolic control and cardiovascular health (elegantly reviewed by Roberts *et al*³⁰). While all of these different experimental maternal obesity paradigms have merit in elucidating various mechanisms contributing to programming, this review aims to focus on the most relevant experimental studies that can be translated to human metabolic control.

Mouse models

Because of its short gestation and genetic homogeneity, the mouse is a commonly used model species for studying developmental programming. Many studies have demonstrated that *in utero* exposure to maternal obesity has adverse metabolic outcomes in offspring, such as poor

fetal growth, metabolic syndrome, and behavioral alterations. Akin to human pregnancy, diet-induced obesity via consumption of a high fat diet (HFD) in pregnant mice alters food intake, substrate utilization, body composition, glucose and lipid metabolism, leptin levels and placenta nutrient transport³¹⁻³⁴. Maternal metabolic dysfunction is likely responsible for programming of metabolic outcomes in offspring. Recent studies point to the influence of insulin resistance per se, in developmental programming. In an elegant approach, insulin receptor substrate-1 (IRS-1) heterozygous dams which are hyperinsulinemic and insulin resistant during pregnancy, but have normal plasma glucose levels and body weight compared to their wildtype counterparts were employed³⁵. Male wildtype offspring from IRS-1 heterozygous dams were glucose intolerant and hyperinsulinemic as early as 1 month of age, had increased liver lipid accumulation, and exhibited hyperresponsive weight when fed an obesogenic diet when compared to male offspring from wildtype dams. Thus, in this model, maternal insulin resistance, in the absence of maternal obesity, induced chronic impairments in lipid metabolism and glucose homeostasis in male offspring³⁵. However, in some mouse models such as glucose transporter-4 heterozygous (GLUT4^{+/-}) females, a model of maternal insulin resistance, consuming a high calorie diet was associated with enhanced lipid clearance but no significant alterations in hepatic glucose or lipid metabolism, suggesting that the mother's ability to adequately metabolize different dietary challenges may play a role in programming offspring development³⁶.

The extent of nutritional insult during gestation also plays a critical role in determining health outcomes in offspring. Long term offspring effects of exposure to maternal obesity include hyperphagia, adiposity, hypertension, insulin resistance, dyslipidemia and hepatic steatosis^{37,38}. Mouse models of maternal HFD consumption during gestation result in obesity, insulin and leptin resistance³⁹⁻⁴¹, hypertension⁴², hepatic steatosis, and non-alcoholic fatty liver

disease (NAFLD) in offspring^{43,44}. For example, adult male offspring of dams fed a high-fat diet during pregnancy and lactation had larger fat depots, increased serum insulin, TNF α and IL1 β , and reduced serum triglycerides. In this same model, the livers of adult male offspring from obese dams had increased phosphorylation of JNK and I κ B kinase and increased PEPCK expression. Moreover, liver triglyceride content was elevated in these offspring as early as one week after weaning and remained elevated into adulthood³⁴. Oben *et al* have also shown that offspring of obese dams present with hepatic steatosis and fibrogenesis, reduced liver IRS-1 expression, and increased phosphorylation of IRS-1, demonstrating that exposure to maternal obesity throughout pregnancy results in an insulin resistant and NAFLD phenotype when compared to offspring of lean dams⁴⁴.

Rat models

Several rat strains including Sprague-Dawley and Wistar rats are commonly used to study the effects of nutritional status during pregnancy and its effects on short term and long term offspring health. Compared to mouse models, rats offer the advantage of being larger in size, easier to handle and having greater fetal and placental size. In contrast to most mouse strains used in research, Sprague-Dawley and Wistar rats are outbred strains and provide greater genetic heterogeneity similar to humans. There is a strong body of literature demonstrating that maternal HFD exposure in rats produces a similar metabolic phenotype in offspring as is seen in mouse models. For example, adult male offspring of Sprague-Dawley dams fed HFD during gestation exhibited classic metabolic syndrome symptoms such as increased body weight and hyperinsulinemia, hyperglycemia and increased triglyceride levels⁴⁵, consistent with findings reported in various mouse models^{34,46,47}. Even mild maternal over-nutrition, independent of the level of pre-conception obesity, has been shown to induce increased adiposity, glucose

intolerance, hyperinsulinemia and altered hypothalamic appetite regulators in rodent offspring^{48,49}.

Studies from our group have utilized a unique overfeeding-based rat model to study maternal obesity at conception and its consequences on offspring development and growth. In this model, female Sprague Dawley rats are overfed in a controlled manner *via* total enteral nutrition, thus maintaining macronutrient content of the diet and bypassing the satiety response that normally limits ad libitum food intake. Pups are cross-fostered at birth to lean dams to limit maternal obesity exposure to the *in utero* period. Using this model, we have replicated many of the classic symptoms of human metabolic syndrome. This model is unique as it avoids parental genetic influences, matches gestational weight gain, limits the exposure of maternal obesity to the *in utero* period, and controls for lactation efficiency, all of which can be confounding variables in studies with human subjects. For these reasons, this model specifically examines the effect of maternal adiposity independently of dietary fat on offspring metabolic health⁵⁰. While birth weight and body weight at weaning (postnatal day 21) was not different in offspring from lean and obese dams, male offspring from obese dams were hyper-responsive (gained more weight and body fat) when challenged with a HFD (45% calories from fat) compared to offspring from lean dams. Moreover, at weaning before HFD challenge and changes in body weight, offspring from obese dams had a lipogenic transcriptomic signature in the liver and white adipose tissue, decreased serum adiponectin, and altered insulin signaling compared to offspring from lean dams⁵¹. Offspring from obese dams also demonstrate decreased basal energy expenditure and impaired ability to oxidize fats. This altered metabolism is also associated with alterations in expression of genes involved in mitochondrial plasticity (fusion and fission) and circadian rhythms⁵². Further characterization of this model demonstrated that maternal obesity at

conception increased proinflammatory gene expression in the uterine environment and male blastocysts as early as day postcoitum 4.5, suggesting that the programming effects of maternal obesity occur very early in development. Likewise, alterations associated with maternal obesity persist during late gestation and are reflected in placental gene expression changes. The influence of obesity on the placenta is unique with the individual placental compartments, with immune response being predominantly affected in the labyrinth zone. High fat diet exposure during pregnancy in rats has also been shown to reduce fetal growth and alter the placental structure by reducing the placental junctional zone with no differences in gene expressions such as PPAR- γ and VEGF⁵³. While a decrease in fetal growth after in utero exposure to maternal high fat diet may seem contradictory, in a subset of obese women, maternal obesity is also a risk factor for SGA^{54,55}, mostly because maternal obesity increases the risk for hypertensive disorders of pregnancy, placental dysfunction, and fetal growth restriction. Moreover, a recent meta review by Faucher and Barger suggest that inadequate GWG and the severity of maternal obesity play important roles in the risk of delivering a SGA baby⁵⁶.

A number of studies in rats have examined long term health outcomes of *in utero* exposure to maternal obesity. Nivoit *et al* observed that at 12 months of age, male and female offspring from obese dams were hyperphagic, heavier and had increased fat pad weights compared to offspring from dams fed standard chow. In addition, euglycemic–hyperinsulinemic clamp at 10-11 months of age revealed that male offspring from obese dams were insulin resistant⁵⁷. Other consequences of exposure to maternal obesity include an amplified and prolonged neonatal leptin surge, elevated leptin mRNA expression in abdominal white adipose tissue, and central leptin resistance that is observed as early as PND 30 (before offspring themselves become obese) and maintained throughout adulthood (PND 90)⁴⁵. Thus, these studies suggest that *in utero* exposure to maternal

obesity induces a prolonged release of abnormally high levels of leptin in neonatal rats, leading to leptin resistance and interfering with hypothalamic functions in the arcuate nucleus and the hypothalamic paraventricular nucleus to program hyperphagia and the development of obesity in these offspring⁴⁵. In conclusion, studies in rats recapitulate many of the long term health outcomes of *in utero* exposure to maternal obesity observed in humans and have been invaluable in elucidating mechanisms of metabolic programming.

Sheep models

While sheep models are used less frequently than rodent models, they are a precocial species like humans, and in sheep, exposure to maternal obesity predisposes offspring to altered growth and metabolic consequences. When ewes were overfed to induce obesity at conception and throughout gestation, mid-gestation fetuses from obese ewes were macrosomic, hyperglycemic, and hyperinsulinemic and exhibited markedly increased pancreatic weight and β -cell numbers compared to fetuses of ewes fed normally. These data also demonstrated the differential impacts of maternal obesity on fetal pancreatic growth and β -cell numbers during early and late gestation. During the first half of gestation there was a marked increase in fetal pancreatic growth, β -cell proliferation, and insulin secretion, followed by a reduction in fetal pancreatic growth and β -cell numbers, resulting in reduced fetal circulating insulin at end of pregnancy⁵⁸.

As with rodent studies⁵⁹, maternal obesity and increased maternal nutrient intake before and during gestation in sheep results in altered growth, adiposity, and glucose tolerance in adult offspring^{59,60}. Maternal over-feeding in late gestation increases PPAR γ -activated genes in fetal visceral fat and also increases subcutaneous fat in postnatal lambs. Enzymes involved in fatty acid biosynthesis, and fatty acid and glucose transporters are also increased in adipose tissue in

response to *in utero* exposure to maternal obesity^{61,62}. Over-nutrition during the preconception stage increases total body fat mass in both male and female lambs^{59,61}, with a predominant effect in visceral fat depots. This suggests that early programming of adult obesity may require overfeeding during pre-conception as well as gestation periods⁵⁹. Similar to rodents and humans, *in utero* exposure to maternal obesity also causes metabolic changes in offspring skeletal muscle. Skeletal muscle insulin is decreased in lambs from obese ewes, while phosphorylation of PKC and IRS-1 is decreased. In addition, lambs from obese ewes have more intracellular adipocytes, higher PPAR γ expression in skeletal muscle and higher intramuscular collagen content, suggesting that maternal obesity impairs offspring skeletal muscle function⁶³. Nicholas *et al* observed lower skeletal muscle GLUT4 and phosphorylated GSK3 α , but increased total GSK3 α in offspring from obese ewes, suggesting that since GSK3 α is a negative regulator of insulin activation of glycogen synthesis, maternal obesity may impair muscle function by interfering with glycogen synthesis⁶³. Maternal obesity also has detrimental effects of offspring cardiac tissue. In fetal hearts from obese ewes, phosphorylation of AMPK and activity of PI3K-Akt was decreased, while p38 MAPK, JNK and IRS-1 phosphorylation was increased⁶⁴. Moreover, maternal obesity was associated with greater accumulation of connective tissue in the fetal heart via increased TGF β -p38 MAPK signaling, suggesting that offspring of obese ewes are predisposed to cardiac dysfunction⁶⁵. How maternal obesity affects hepatic function in sheep has been significantly less studied. In another study by Nicholas *et al*, they observed that offspring of obese ewes had increased epigenetic regulators of hepatic insulin signaling (miR-29b, miR-102 and miR-107), decreased IR, and decreased phosphorylation of Akt and FOXO1, suggesting that maternal obesity does indeed alter hepatic metabolism in sheep⁶³. Interestingly, a classic consequences of maternal obesity in rodent models -increased neonatal leptin is not seen in ovine

models as neonatal lamb plasma leptin levels are not altered in conjunction with maternal obesity status⁶⁰.

Non-human primate models

Non-human primates have been used as a model to study the effect of maternal obesity for the past thirty years. In the baboon, overfeeding during the pre-weaning period permanently increased adiposity in offspring as a result of fat cell hypertrophy in a gender-dependent manner in the females only⁶⁶. Consistent with other animal models of maternal obesity, maternal HFD exacerbates lipotoxicity in the fetal liver of macaques and predisposes the offspring to develop nonalcoholic fatty liver disease in adulthood⁶⁷. There are also considerable similarities in placental and fetal phenotypes between normal weight offspring of obese baboons and large-for-gestational age human fetuses⁶⁸. Consistent with findings from rat models, Grayson *et al* showed that fetuses from mothers on HFD exhibited up-regulated proopiomelanocortin mRNA expression and down-regulation of agouti-related protein mRNA compared to fetuses from control diet fed mothers⁶⁹. Recently, Sullivan *et al* demonstrated that chronic consumption of a HFD during gestation disturbs the serotonergic system and increases anxiety-like behavior in nonhuman primate offspring⁷⁰. In the Japanese macaque, HFD feeding during pregnancy, independent of maternal obesity, increased placental inflammatory cytokines and the expression of Toll-like receptor 4⁷¹. HFD feeding also resulted in a significant increase in the frequency of both placental infarctions and stillbirth, possibly because of reduced blood flow on the fetal side of the placenta. These results suggest that HFD, independent of obesity, affects uterine blood flow and insulin resistance, further exacerbating placental dysfunction and resulting in an increased frequency of stillbirth⁷¹.

Evidence for long-term influences from human studies

Several human and rodent studies provide strong evidence for the transmission of obesity from mother to offspring (human studies summarized in **Table 1**). Both maternal under- and over-nutrition positively correlate with offspring adiposity later on in life. The earliest evidence that maternal metabolic state influences birth weight and risk of obesity in offspring comes from studies in Pima Indians. In a study of discordant sibships, Dabelea and colleagues clearly showed that intrauterine exposure to maternal diabetes increases offspring's risk of diabetes and obesity⁷². Likewise, in a large population-based birth cohort, increasing trends of being born large-for-gestational age (LGA) at birth were strongly associated with greater maternal BMI. Since being LGA at birth significantly increases risk of obesity in adolescence and adulthood, LGA risk has been widely studied in numerous studies. Children of obese mothers that were born LGA are at twice the risk of developing insulin resistance accompanying childhood obesity⁷³. In a recent meta-analysis of over 20 studies, high maternal BMI was unequivocally associated with LGA risk. Even in the absence of maternal diabetes or glucose intolerance, seminal work from Catalano and colleagues showed that maternal obesity contributed to greater adiposity and insulin resistance in the fetus. These changes in offspring insulin resistance in response to maternal obesity persist into childhood⁷³ and early adulthood⁷⁴. Early findings from the Southampton Women's survey also showed positive associations between maternal BMI and neonatal adiposity. These findings have now been independently confirmed in the context of the larger Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, which showed that maternal BMI independent of glycemia is strongly associated with excess fetal growth and adiposity⁷⁵⁻⁷⁷. An American cohort of 854 participants showed that parental obesity increases the risk of adult obesity by two fold⁷⁸. Greater adiposity associated with maternal obesity persists in childhood and adolescence, as shown from findings from the ALSPAC and Mater-University

studies. Moreover, in young adults, maternal obesity is associated with an adverse lipid profile⁷⁹. Recently Aris *et al*, showed that gestational fasting plasma glucose (FPG) was positively associated with birth weight. Gestational FPG and pre-pregnancy obesity interacted significantly for the association with offspring growth and overweight status in the first 36 months of life. In non-obese mothers, each unit increase in gestational FPG was associated with increased offspring weight and BMI as well as increased risk of overweight in the first 36 months of life. However, in obese mothers, each unit increase in gestational FPG was associated with decreased offspring weight and BMI velocity and decreased risk of overweight in the first 36 months of life⁸⁰. Prepregnancy adiposity was associated with offspring growth in early childhood. Although pooled analyses showed no demonstrable difference by 3 months of age, there were contrasting and opposite associations of gestational glycemia with weight and BMI in the first 36 months of life in offspring of nonobese and obese mothers separately⁸⁰. In the Generation R study, maternal obesity was associated with an increased risk of childhood overweight and a clustering of cardiometabolic risk factors at 6 years of age^{78,81}. Maternal obesity correlates with higher offspring blood pressure in children⁸²⁻⁸⁴ and teenagers⁸⁵, increased risk of asthma and wheezing in children⁸⁶ and adolescents⁸⁷, as well as decreased cognitive performance (of modest effect size) in children ages 5-7⁸⁸ and increased risk of affective problems such as depression in children from ages 5-17⁸⁹. Maternal obesity is also associated with an increase in adipogenic potential in umbilical cord mesenchymal stem cells, demonstrating that programming effects of maternal obesity are present at birth and persistent in fetal tissues even after removal from the maternal obesity milieu⁴⁶. Therefore, while there is considerable evidence that maternal obesity during pregnancy increases adiposity at birth^{28,75}, during childhood^{90,91}, and during adolescence⁹², comprehensive longitudinal studies assessing the impact of *in utero* exposure to

maternal obesity in adult, offspring are lacking. An American cohort of 854 participants showed that parental obesity increases the risk of adult obesity by two-fold⁷⁸. In a record linkage cohort, Reynolds *et al* demonstrated that maternal obesity was associated with all-cause mortality and hospital admission for a cardiovascular event in adult offspring⁹³. Thus while there is considerable evidence suggesting that a short period of over-nutrition during gestation can affect health throughout life, the long term consequences of maternal obesity on adult offspring health is an area that could benefit greatly from further research.

4. Mechanisms of offspring metabolic programming

A large number of studies have focused on elucidating underlying mechanisms contributing to metabolic programming associated with maternal diet and obesity. Broadly, data from experimental models implicates both changes in energy and nutrient metabolism, and alterations in appetite and food preference in mediating physiological changes such as adiposity and metabolic dysfunction. Most studies in animal models have focused on changes associated with high-fat diets. However, it is becoming increasingly evident that other caloric excesses from high fructose and high-fat/high-sucrose diets also lead to permanent programming. While the evidence for high maternal BMI is quite clear, the relative contribution of dietary components, macronutrient or otherwise in the context of human obesity still remains unclear.

Fetal Over-nutrition: the Pedersen hypothesis and beyond

Abnormally high maternal glucose during pregnancy as evident in women with type 1 or type 2 diabetes is characteristically associated with increased fat deposition *in utero*. In the 1950s, while primarily caring for women with type 1 diabetes, Jorgen Pedersen surmised a potential mechanisms linking maternal diabetes to fetal macrosomia involving transplacental transfer of glucose⁹⁴. In this model, maternal hyperglycemia led to excess exposure of the fetus

to maternal glucose, fetal hyperinsulinemia and excess growth. Freinkel and Metzger later added a potential role of other dietary constituents on fetal development during diabetic and obese pregnancy⁹⁵. Likewise, Schwartz *et al* reported fetal size to be significantly correlated with umbilical cord blood total insulin, free insulin and C-peptide content⁹⁶. Results from the large multi-center HAPO study also showed a linear relationship between increasing maternal glucose and cord C-peptide levels with birth weight⁷⁷. Similar evidence from classic studies in animal models also concurs with the Pedersen hypothesis. For example, acute injection of insulin into rat fetuses led to increased fetal weight as compared to saline-injected controls⁹⁷. In addition, *in utero* insulin infusion via an osmotic mini-pump implanted into fetal rhesus monkeys for 21 days led to a 34% increase in body weight, as compared to controls despite normal glucose levels in mothers⁹⁸. Conversely, the effect of lower insulin levels on fetal body growth was reported by Phillips *et al*, where injection of streptozotocin to destroy β cells was associated with subsequent maternal hypoinsulinemia and a 21% reduction in fetal body weight⁹⁹.

Placental nutrient sensing

The placenta plays a critical role in fetal growth and development because of its role in nutrient transport, hormone production and immunologic barrier function. The placenta integrates information from both the mother and baby to match fetal growth to maternal nutrient supply by altering maternal physiology, placental growth and placental nutrient transport^{100,101}. Increasing evidence suggests that perturbations in maternal physiology, such as (but not limited to) hypoxia, stress, obesity, diabetes, and toxins, can influence placental structure and function, altering nutrient and oxygen supply, methyl donor levels, hormone secretion and release of other signaling molecules into the fetal circulation. For example, maternal hormones such as insulin, leptin and IGF-1 positively regulate placental amino acid transport, whereas maternal cortisol

inhibits placental amino acid transport. Several studies in humans support the idea that maternal supply is an important regulator of placental function. System A non-essential amino acid transport was increased in placenta of large babies from obese mothers¹⁰² and maternal obesity was associated with an increase in the glucose transporter GLUT-1 in placenta of large babies¹⁰³. In a mouse model of HFD prior to and during pregnancy that results in fetal overgrowth, similar increases in placental System A amino acid transport and GLUT-1 were observed⁴⁶. Moreover, maternal adiponectin infusion in obese dams from embryonic day 14.5 to embryonic day 18.5 reversed the effects of maternal diet-induced obesity on placental function and fetal overgrowth¹⁰⁴. Thus, because the placenta integrates information from both the mother and baby and responds by altering its structure and function to optimize mother and baby's health at birth, it plays a critical role in developmental programming.

Inflammation/LPS

Adipose tissue inflammation is another possible mechanism by which maternal obesity status could affect offspring health¹⁰⁵. Adipose tissue is composed of multiple cell types, including adipocytes (fat cells) and the stromal vascular fraction (SVF), which includes preadipocytes, fibroblasts, endothelial cells, and immune cells¹⁰⁶. Adipose tissue is an endocrine organ which secretes several types of adipokines and cytokines¹⁰⁷. Excess adipose deposition during pregnancy leads to impaired regulation of adipokine and cytokine secretion and contributes to the development of obesity-induced comorbidities such as insulin resistance and metabolic syndrome¹⁰⁸⁻¹¹⁰. Adipose tissue inflammation is characterized by infiltration of immune cells including monocytes/macrophages, neutrophils, B-Lymphocytes and T Lymphocytes¹¹¹⁻¹¹³. The role of chronic low-grade inflammation in obese mothers has become an emerging focus in the developmental programming field.

Inflammation during gestation is linked to the activation of many inflammatory pathways, including Nod-like receptors (NLRs), NLR family, pyrin domain containing 3 (NLRP3) inflammasome, PPAR signaling and the NF- κ B pathway^{31,114}. Several studies have demonstrated that unbalanced maternal nutrition results in meta-inflammation in the mother and programs inflammation in offspring tissues^{115,116}. There is now strong evidence that early changes in inflammatory markers can be predictors of later metabolic and cardiovascular diseases, thus evaluation of offspring inflammatory profiles at early stages of development may prove to be useful biomarkers for later life metabolic diversity. However, further exploration is needed to understand fully how these pathways contribute to developmental programming.

Maternal immune activation during pregnancy *via* lipopolysaccharide (LPS) has been shown to modify the immune response of offspring^{117,118}. LPS activation led to more M1 (proinflammatory) bone marrow-derived macrophages¹¹⁷ and enhanced serum IL-1 β production upon immune challenge in adulthood¹¹⁸. Moreover, placenta from obese pregnant mothers showed increased macrophage infiltration and proinflammatory gene expression compared to placenta from lean mothers¹¹⁹. Infiltrating macrophages and other immune cells secrete inflammatory cytokines into the maternal and fetal circulations, possibly affecting fetal development and health outcomes. It is speculated that this is a contributing mechanism for the programmed alterations in offspring metabolism associated with increased adiposity and insulin resistance. As mentioned earlier, the placenta is responsible for nutrient transport and nutrient sensing from mother to fetus and vice versa, and thus plays a critical role in fetal development. The placenta transports free fatty acids from the maternal circulation to the fetal circulation for uptake by the fetal liver, where they are esterified and released as triglycerides into the circulation¹²⁰ and increased maternal triglycerides correlated with fetal macrosomia¹²¹. In another study, Zhu *et al* observed elevated free fatty acids,

cholesterol, and triglycerides in fetal circulation from obese ewes which was accompanied by upregulation of toll-like receptor 4 (TLR4), NF- κ B, and JNK signaling in placental cotyledon tissue¹²². These findings suggest that greater fatty acid uptake by the placenta activates inflammatory pathways in the placenta. Therefore, the state of chronic low-grade inflammation in pregravid obesity persists throughout pregnancy and contributes to an inflammatory environment for the developing fetus¹²³. Our group has demonstrated that maternal obesity is associated with changes in placental transcriptome which correspond with increased placental lipid, oxidative stress and inflammation. We observed that obesity-induced placental lipotoxicity is mediated through JNK signaling. Moreover, a lipotoxic placental environment may impact placental development and function, as demonstrated by decreased angiogenic factors and altered umbilical cord blood nutrients, leading to metabolic programming in the offspring¹²³.

Gestational Weight Gain (GWG)

Gestational weight gain over the course of pregnancy has sharply increased over the past few decades, along with the parallel increase in obesity prevalence. GWG has been proposed as an alternative mechanism for adverse health outcomes in a child's long-term health. Adiposity in early adulthood is influenced by prenatal influences such as maternal adiposity, greater gestational weight, and parity independent of current lifestyle factors. In a population-based cohort, greater GWG was shown to be associated with greater offspring BMI and higher systolic blood pressure in early adulthood. In this cohort, offspring BMI at 21 years of age was on average 0.3 kg/m² higher for each 0.1-kg/wk greater GWG after adjustment for potential confounding factors. Systolic blood pressure also was greater in offspring whose mothers had higher GWG¹²⁴. Oken *et al* reported that greater weight gain during pregnancy is associated with higher child BMI z-score, sum of subscapular and triceps skinfold thicknesses and systolic blood

pressure. Compared with inadequate weight gain, women with adequate or excessive weight gain had children with higher BMI z-scores and risk of overweight¹²⁵. Offspring from mothers with higher BMI at the first antenatal visit and offspring whose mothers were primiparous had higher body fat percentage. Higher offspring percentage body fat was also independently associated with higher pregnancy weight gain. There were similar significant associations of increased maternal BMI, greater pregnancy weight gain, and parity with greater offspring waist circumference, BMI, and fat mass index¹²⁶. Increased maternal BMI was associated with increased neonatal fat mass, fat-free mass, and percentage of body fat. An increase in predicted GWG was associated with increased fat mass, fat-free mass, and percentage of body fat. GWG at different stages of pregnancy were independently associated with fat mass and percentage of body fat in neonates¹²⁷. It is well established that higher gestational weight gain is not only associated with long term outcomes such as childhood obesity but also increases risk for pregnancy complications such as cesarean delivery, complicated vaginal delivery, preterm delivery, and fetal macrosomia¹²⁸⁻¹³¹. Recent large population-based studies suggest that the ideal range of weight gain for optimal outcomes at delivery should be lower than is currently recommended, especially for overweight and obese women¹²⁹.

Epigenetics

A widely hypothesized overarching mechanism linking *in utero* exposure to later life health is via epigenetic modification of offspring DNA or regulators of chromatin structure such as histone modifications during critical periods of development. The traditional definition of “epigenetic” modifications are mitotically heritable alterations in gene expression that occur without changes to the DNA coding sequence¹³². More recently, the definition of epigenetics has been broadened to encompass heritable, environmentally acquired, and transgenerational

(meiotic) epigenetic alterations. Epigenetics has been established as a driving mechanism for many chronic diseases such as cancer¹³³, neuro-degeneration¹³⁴ and metabolic complications¹³⁵. Epigenetic modifications can occur through several mechanisms: DNA methylation, histone modifications, DNA-binding proteins (i.e. autoregulatory transcription factors), and non-coding RNA, and these epigenetic modifications occur synergistically throughout development to allow for differentiation of diverse cell types. Although the science behind epigenetic regulation has gained momentum in the past few years, the precise epigenetic mechanisms governing mammalian developmental programming still remain unclear.

In mammals, DNA methylation in differentiated cells occurs at cytosines in the CG context (CpGs) (where “p” stands for the intervening phosphate group), converting cytosine to 5-methylcytosine. Following DNA replication, the DNA methyltransferase 1 (DNMT1) ensures maintenance of the original pattern of CpG methylation in the daughter strands, providing a simple mechanism for the perpetuation of epigenetic information in proliferating cells. CpG rich regions are non-uniformly distributed over the genome and generally referred to as ‘CpG islands’ and are prominently found in promoters of genes. While most CpG islands in promoters show low methylation levels, flanking regions of islands called CpG shores have intermediate methylation status and have been suggested to be important in gene regulation. Overall, CpG methylation impacts gene expression by binding to methylation-sensitive DNA binding proteins and interacting with various modifications of the histone tails that regulate DNA accessibility¹³⁶. More recently, microRNA regulation of gene expression has also been identified as a mechanism responsible for epigenetic modifications and evidence suggests microRNAs may play a role in regulation of DNA methylation¹³⁷. DNA methylation is the most well characterized epigenetic mechanism for several reasons. First, DNA methylation is established early in development and

is mitotically inherited. Second, DNA methylation is highly stable in differentiated cells and is stable during tissue collection and storage procedures. Third, methylation status can easily be measured from small samples. There are several animal studies and an increasing number of human studies demonstrating that epigenetic dysregulation can cause obesity.

A classic example of epigenetically-mediated obesity in an animal model is the *Agouti* *viable yellow* (A^{vy}) mouse. The *agouti* gene is normally expressed in hair follicles and regulates coat color, and the A^{vy} mutation results from a spontaneous transposition of a retrotransposon upstream of the *agouti* gene. Stochastic and systemic inter-individual variation of DNA methylation at A^{vy} causes ectopic *agouti* expression in various tissues including the hypothalamus. The *agouti* protein is structurally similar to agouti-related protein (Agrp), thus ectopically expressed *agouti* protein competes with Agrp binding to the melanocortin 4 receptor in the hypothalamus and induces epigenetically-mediated hyperphagic obesity¹³⁸. The A^{vy} locus is considered to be a metastable epiallele (ME), that is, a loci where DNA methylation occurs stochastically early in embryogenesis that is maintained and stably propagated during differentiation^{139,140}. This stochastic establishment of epigenotype leads to systemic interindividual variability in DNA methylation that is neither cell-type specific or genetically mediated. These MEs are sensitive to environmental influences, such as maternal nutrition in early pregnancy. For example, in the A^{vy} mice, promethylation dietary supplementation prevented maternal obesity-mediated transgenerational transmission of obesity. In humans, candidate MEs have been identified by comparing genome-scale methylation profiles of DNA between different tissue samples from the same individual and from monozygotic twin studies. Moreover, nutritional status early in pregnancy has been linked to persistent epigenetic changes in offspring

MEs as elegantly shown in a study from rural Gambia where seasonal fluctuations in dietary intake occur^{141,142}.

While the epigenetic effects of fetal under-nutrition have been widely studied, fewer epigenetic studies have focused on the effects of over-nutrition or maternal obesity during pregnancy. The Epigenetic Birth Cohort out of Brigham and Women's Hospital in Boston studied 319 newborns and found no correlation between maternal prepregnancy BMI and Long interspersed nuclear elements-1 (LINE-1) methylation (a global measure of DNA methylation) in placenta or umbilical cord blood DNA¹⁴³. However, in another cohort of 57 mother/infant dyads, maternal BMI positively correlated with DNA methylation of the peroxisome proliferator activated receptor gamma, co-activator 1 alpha (*PPARGC1A*) promoter in umbilical cord DNA¹⁴⁴. Also, infants born to obese mothers with gestational diabetes have decreased methylation at nuclear receptor subfamily 3 group C1 (*NR3C1*), the gene encoding the glucocorticoid receptor and the imprinted gene mesoderm specific transcript (*MEST*)¹⁴⁵. Thus, maternal obesity-associated alterations in offspring DNA methylation patterns is likely to be loci and tissue specific. Another important question in the field is for how long do these maternal obesity-associated alterations in offspring DNA methylation patterns persist? To address this issue of persistence, Godfrey *et al* designed a prospective study to relate umbilical cord DNA methylation with adiposity at age 9. They observed that umbilical cord methylation of a specific CpG in the retinoid X receptor alpha (*RXRA*) gene inversely correlated with maternal carbohydrate consumption in early pregnancy and positively correlated with the child's adiposity at age 9¹⁴⁶. There is also epidemiological evidence that paternal obesity status at conception contributes to the offspring's risk of developing obesity, but there is a paucity of information regarding how this may occur. In a recent manuscript by Soubry *et al*, the imprinted genes

MEST, paternally expressed 3 (*PEG3*) and neuronatin (*NNAT*) were hypomethylated in umbilical cord blood DNA of neonates from obese fathers, independent of maternal obesity status. They also observed that *PLAGL1* was hypermethylated and maternally expressed 3 (*MEG3*) was hypomethylated in neonates from obese mothers¹⁴⁷. Chen *et al* demonstrated in a mouse model of paternal high fat diet, sperm tRNA-derived small RNAs (tsRNAs) impaired offspring glucose tolerance and induced insulin resistance, but had no effect on offspring bodyweight¹⁴⁸. Collectively, these studies demonstrate that both maternal and paternal obesity status can cause epigenetic disruption in the offspring that predisposes them to develop obesity or metabolic disease later on in life.

Microbiome

The latest developments in microbiome research have established that the microbiome interacts with nearly every physiological system and is a possible mechanistic pathway linking maternal habitus during pregnancy and lactation to childhood health. The human body harbors trillions of bacteria. Most of these microbes reside symbiotically within the host gastrointestinal tract (GI) and are intricately involved in functions such as metabolism of indigestible polysaccharides, essential nutrient production, and protecting the GI tract from colonization by pathogenic bacteria^{149,150}. The gut microbiota also plays a critical role in regulating host adipose accumulation. For example, when germ-free mice were colonized with microbiota from normal mice, these mice exhibited pronounced increases in adiposity and *de novo* lipogenesis¹⁴⁹. Moreover, germ-free mice colonized with microbiota from obese mice had greater increases in adiposity compared to germ-free mice colonized with microbiota from lean mice¹⁵¹. In both humans and mice, the most abundant phyla are Firmicutes and Bacteroidetes and from studies of genetically obese mice and lean and obese twins, it was shown that obesity is associated with a

change in microbiome composition, namely an increase in Firmicutes and a decrease in Bacteroidetes¹⁵²⁻¹⁵⁴. Thus, it is appreciated that gut dybiosis is associated with weight gain and altered metabolism associated that accompanies obesity^{153,155}. While the role of the microbiome in several biological functions is becoming clearer every day, we still lack an understanding of how the offspring microbiome is established and affected by maternal habitus or diet. Maternal gut bacterial load increases over the course of pregnancy and there is a significant change in gut microbiome composition from the first to third trimester of pregnancy¹⁵⁶⁻¹⁵⁸. The increased bacterial diversity as pregnancy develops corresponds with known changes in insulin resistance and inflammation during the progression of normal pregnancy¹⁵⁹. In rodents, manipulating the maternal gut microbiota during pregnancy, either through broad spectrum antibiotic or probiotic administration, has marked effects on offspring GI tract development (reduced stomach growth and acid secretion, increased intestinal permeability) and amount of Enterobacteriaceae in cecal contents¹⁶⁰. While pre-pregnancy maternal weight and gestational weight gain are associated with alterations in gut microbiome composition, different cohorts report conflicting results. Collado *et al* observed that overweight pregnant women had increased levels of *Bacteroides* and *Staphylococcus*¹⁵⁶, while Santacruz *et al* observed an increase in *Staphylococcus* and *Escherichia coli*, but a decrease in *Bacteroides* and *Bifidobacterium* in overweight pregnant women¹⁶¹. Importantly, several studies suggest that maternal obesity-associated GI dybiosis alters fetal GI development and microbiota composition. In offspring of rat dams fed a Western diet during pregnancy and lactation, an increase in the Firmicutes:Bacteroidetes ratio and altered immune response was observed¹⁶². Moreover, in a clinical study, maternal obesity was associated with greater homogeneity in the gut microbiome composition of offspring from mothers of higher socioeconomic status (SES). Also in the higher SES group, children born to obese versus non-

obese mothers had differences in abundances of several species of bacteria which are linked to differences in weight and diet¹⁶³. An elegant study by Ma *et al* in a non-human primate model of maternal high fat diet during pregnancy suggests that diet, not obesity, is the determinant of the GI microbiome¹⁶⁴. In this study, female macaques were fed either an isocaloric high fat diet (HFD) or a control diet during pregnancy and lactation. Some of the female macaques were sensitive to the high fat diet and gained more weight and developed insulin resistance compared to others that were resistant to the metabolic effects of the HFD. Interestingly, after characterizing the maternal GI microbiome, the HFD females grouped together, separately from the control diet fed females, independent of their metabolic response to HFD, suggesting that diet was the driving force for determining GI microbiome composition. Moreover, offspring from macaques fed HFD during pregnancy and lactation exhibited microbial dysbiosis that was only partially corrected by a postweaning control diet. In conclusion, there is strong evidence that *in utero* exposures play an important role in shaping the offspring microbiome. There are still many gaps in our knowledge of how the maternal gut microbiota shapes a child's microbiome and eventually their short-term and long-term health outcomes.

5. Interventions

In experimental models of maternal obesity, strategies to reduce the detrimental offspring effects of maternal obesity include maternal dietary interventions and maternal exercise paradigms before and during pregnancy, as well as pharmacological treatments during pregnancy. As mentioned earlier, one significant concern regarding experimental models of maternal obesity exposure is that there is not a standard protocol or diet for inducing maternal obesity in animal models. Moreover, when performing exercise interventions, questions regarding the translatability of rodent wheel running to human exercise arise. For these reasons

this section will focus on interventions in humans that involved participants partaking in an actual diet or exercise regimen or counseling, and will not cover studies that included self-reported diet and activity measures. Two excellent reviews on animal model interventions for maternal obesity can be found here: Nathanielsz *et al*¹⁶⁵ and Penfold *et al*¹⁶⁶.

In humans, recent efforts have focused on a number of strategies including dietary counseling, physical activity and behavior modifications to limit excessive GWG and mitigate the detrimental programming effects of maternal obesity. While these lifestyle modifications, alone or in combination may be moderately successful in reducing GWG, these interventions have not proven successful in reducing fetal macrosomia, GDM or preeclampsia in obese pregnant women. For example, in the randomized clinical trial Pregnancy and Glycemic Index Outcomes study, women <20 weeks of gestation were offered low glycemic index advice or healthy eating advice, but there were no differences in birth weight or ponderal index¹⁶⁷. Similarly, in the Lifestyle in Pregnancy (LiP) study, obese women early in pregnancy were randomized to a lifestyle intervention or control group. The lifestyle intervention program included dietary guidance, free gym membership, physical training and coaching. While the lifestyle intervention successfully limited GWG in obese pregnant women, there were no differences in obstetrical and neonatal outcomes compared to the control group¹⁶⁸. Moreover, the LIMIT randomized trial in Australia provided dietary and exercise counseling for overweight and obese women at 10-20 weeks gestation and there was no difference in the incidence of delivering a LGA baby compared to the standard of care¹⁶⁹. In the Treatment of Obese Pregnant Women (TOP) study, obese pregnant women were randomized to a physical activity (pedometer) and dietary intervention group, a physical activity only group or a control group at 11-14 weeks gestation. While both interventions significantly lowered GWG, there were no differences in

birth weight between the three groups¹⁷⁰. It is unclear what the long-term effects of these lifestyle interventions are on the offspring's risk of developing obesity and metabolic dysfunction. It is likely that the timing of these interventions is critical since there are many lipogenic and inflammatory changes that begin very early on in the first trimester of pregnancy. Thus, results from current randomized clinical trials suggest that lifestyle interventions that occur before pregnancy may be more effective at mitigating the detrimental programming effects of maternal obesity.

Conclusions

Maternal obesity is increasingly being recognized as a critical determinant of numerous offspring health outcomes. Key among these is risk of metabolic dysfunction, greater birth weight and increased obesity risk in later-life thereby promoting a vicious cycle. Increasing evidence also suggests alterations in neurological and cognitive phenotypes in offspring. Animal studies provide unequivocal evidence for this phenomenon and also shed light toward possible mechanisms, which include direct effects of obesity-associated metabolic dysfunction and persistent effects via modulation of the epigenome. While much of this mechanistic insight might translate to the human situation, key challenges in the respective roles of maternal diet, gestational weight gain and attendant life-style factors such as physical activity that closely associate with obesity remain to be elucidated.

701   **ACKNOWLEDGEMENTS**

702   The authors are supported in part by the USDA Agriculture Research Service CRIS
703   6251-51000-010-05S.

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707 Table 1. Evidence for long-term influences of maternal obesity from human studies

Factor	Findings	Reference
Gestational Environment and Offspring Obesity	Intrauterine exposure to maternal diabetes increases offspring's risk of diabetes and obesity in Pima Indians Discordant Sibships	Dabelea <i>et al.</i> ⁷²
	Increasing trends of LGA birth were strongly associated with maternal BMI in large population based cohort	Surkan <i>et al.</i> ¹⁷¹
	LGA offspring born to GDM mothers have 2-fold higher risk of Metabolic syndrome at 11 years of age, also identified an independent risk of maternal OB	Boney <i>et al.</i> ⁷³
	Maternal over nutrition during the first half of gestation predicts offspring overweight/obesity and abdominal obesity in adolescence,	Laitinen <i>et al.</i> ¹⁷²
	Maternal weight gain during pregnancy increases birth weight independently of genetic factors	Ludwig <i>et al.</i> ^{173,174}
Maternal Obesity and The Neonate	Fetuses of obese mothers have greater adiposity and insulin resistance	Catalano <i>et al.</i> ²⁸
	Maternal triceps skinfold positively associated with increased neonatal fat mass via DEXA	Harvey <i>et al.</i> ¹⁷⁵
	Maternal BMI independent of glycemia is strongly associated with excess fetal growth and adiposity	HAPO study ⁷⁶ ; Catalano <i>et al.</i> ⁷⁵
	Late preterm infants born to obese mothers are more likely to be delivered by cesarean section and have larger BWs	Khalak <i>et al.</i> ¹⁷⁶
Maternal Obesity and Childhood Obesity	Among 2-4 year olds maternal obesity in early pregnancy doubled the risk of obesity	Whitaker <i>et al.</i> ⁷⁸
	Offspring of obese mothers showed 4.6 times the risk of being obese at 7 years of age	Reilly <i>et al.</i> ¹⁷⁷
	Maternal BMI associated with increased offspring BMI at 14 years of age; association is stronger for maternal than paternal BMI	Lawlor <i>et al.</i> ⁹²
	Maternal BMI shows stronger correlation GWG to both offspring intelligence and executive function linking maternal obesity to long-term child outcomes.	Pugh <i>et al.</i> ¹⁷⁸

Maternal Obesity and Obesity in Adulthood	Women whose mothers were obese had 6.1-fold greater risk of obesity at 18 years and 23 years of age	Stuebe <i>et al.</i> ¹⁷⁹ ; Tequeanes <i>et al.</i> ¹⁸⁰
	The decreased risk of obesity in children born to obese women following weight loss after bariatric surgery	Kral JG <i>et al.</i> ¹⁸¹
Excessive GWG on Offspring Obesity Risk	Excessive GWG in both normal and OW/ OB women increases offspring obesity	Oken <i>et al.</i> ¹²⁵ ; Hull <i>et al.</i> ¹⁸² ; Crozier <i>et al.</i> ¹⁸³ ; Badon <i>et al.</i> ¹⁸⁴

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Figure

Figure 1