Maternal obesity in females born small: Pregnancy complications and offspring disease risk

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Obesity is a major public health crisis, with 1.6 billion adults worldwide being classified as overweight or obese in 2014. Therefore, it is not surprising that the number of women who are overweight or obese at the time of conception is increasing. Obesity during pregnancy is associated with the development of gestational diabetes and preeclampsia. The developmental origins of health and disease hypothesis proposes that perturbations during critical stages of development can result in adverse fetal changes that lead to an increased risk of developing diseases in adulthood. Of particular concern, children born to obese mothers are at a greater risk of developing cardiometabolic disease. One subset of the population who are predisposed to developing obesity are children born small for gestational age, which occurs in 10% of pregnancies worldwide. Epidemiological studies report that these growth-restricted children have an increased susceptibility to type 2 diabetes, obesity, and hypertension. Importantly during pregnancy, growth-restricted females have a higher risk of developing cardiometabolic disease, indicating that they may have an exacerbated phenotype if they are also overweight or obese. Thus, the development of early pregnancy interventions targeted to obese mothers may prevent their children from developing cardiometabolic disease in adulthood.

Keywords:
Developmental programing / Fetal growth restriction / Insulin resistance / Maternal pregnancy / Obesity

1 Introduction

Obesity is clinically defined as having a BMI over 30 (World Health Organization (WHO) 2015; http://www.who.int/mediacentre/factsheets/fs311/en/), and is associated with an increased risk of developing a number of comorbidities, including cardiovascular and metabolic diseases and nephropathy [1]. A recent report by McKinsey Global Institute stated that obesity is considered one of the top three global social burdens generated by human beings, along with smoking and armed violence, and it is estimated that $2.0 trillion USD is spent worldwide annually as a result of obesity (McKinsey Global Institute 2014; http://www.mckinsey.com/insights/economic_studies/how_the_world_could_better_fight_obesity).

Since 1980, obesity rates worldwide have more than doubled with 2.1 billion people, or nearly 30% of the global population, classified as being obese or overweight in 2013 [2]. Of major concern, there were 42 million children under 5 years of age who are overweight or obese in 2013 according to the WHO (2015).

The dramatic increase in the prevalence of obesity in recent years is suggested to be caused by a poor early life environment, which can have long-term effects on the susceptibility of the developing offspring to develop a wide range of adverse conditions in adulthood. Indeed, there has been a plethora of epidemiological and experimental evidence that strongly suggest that alterations in the in utero environment, due to maternal nutrition, including maternal obesity and maternal undernutrition, programs the developing offspring to develop cardiovascular and metabolic disease later in life [3, 4]. The disturbances during critical stages of development can result in adverse changes in fetal physiology, which predispose the fetus to a number of diseases in adulthood. In fact, other studies relate insults during critical periods of
development to adverse conditions later in life, such as type 2 diabetes [4, 5], hypertension [6, 7], and obesity [8, 9]. The fetus often responds to the poor conditions in an adverse intrauterine environment by undergoing physiological and metabolic adaptations in order to protect the most vital organs, such as brain, at the detriment of other organs [10]. This “thrifty phenotypes hypothesis” suggests that when the postnatal nutritional environment is similar, the individuals would then be able to endure the poor condition, but the adaptations become detrimental when the postnatal nutrition is different than the in utero environment [10, 11].

2 Obesity in pregnancy

Pregnancy is the greatest physiological challenge facing women that results in alterations in maternal physiology and metabolism to assist in fetal growth and development, which is modulated by a number of key molecules [12]. For example, glucose, the primary nutrient crossing the placenta, is important for fetal and placental growth [12, 13]. During pregnancy, glucose homeostasis in the mother is altered so that there is a progressive increase in insulin resistance and gluconeogenic activity to sustain glucose transfer to the fetus [14]. Lipid metabolism is also altered in pregnancy with a significant increase in plasma cholesterol and triglyceride concentrations due to enhanced lipolytic activity and reduced lipoprotein lipase activity of adipose tissue during late gestation [15, 16]. During the first and second trimester, the mother is in an anabolic state whereby an increase in lipogenesis activity and adipose tissue lipoprotein lipase activity causes the mothers fat depots to accumulate [12]. The mother then shifts into a catabolic state during late pregnancy when fetal growth accelerates [17].

In an obese mother, the pregnancy adaptations differ from what occurs in healthy pregnant women. For example, glucose metabolism is significantly altered with an increase in peripheral and hepatic insulin resistance during the first trimester of pregnancy compared to normal weight pregnant women [18]. Therefore, is not surprising that the incidence of gestational diabetes is higher in overweight or obese pregnant women compared to normal weight pregnant women [18].

Obesity is a chronic low-grade inflammatory condition that is characterized by increased adipocyte mass, an increase in fasting whole body free fatty acids, and glycerol released from adipocytes [28]. White adipose tissue produces several proinflammatory cytokines, such as TNF-α and IL-6, which are increased in obesity [29]. Importantly, the placenta also produces these inflammatory cytokines, with the exception of adiponectin [30, 31]. Similar to the upregulation of inflammatory cytokine expression in obese adipose tissue, there is a two- to threefold increase in proinflammatory cytokine expression (IL-1, TNF-α, and IL-6) in the obese placenta, which is likely due to increased macrophage infiltration compared to a healthy pregnant women [32]. Likewise, the plasma concentrations of C-reactive protein, IL-6, and leptin were also increased in pregnant obese women compared to normal weight women [27, 32]. Obese women who were diagnosed with gestational diabetes were reported to have low serum adiponectin, a marker for increased insulin sensitivity, at 24–28 wk of pregnancy compared to women with obesity alone [33]. Thus, these studies demonstrate that maternal obesity is associated with increased inflammatory mediator expression in the maternal plasma and placenta, which may contribute to an inflammatory in utero environment for the developing fetus.

3 The effects of maternal obesity on offspring health

It is well established that maternal obesity is associated with increased fetal growth, which can lead to offspring being born macrosomic [34]. However, recent findings suggest that offspring born to obese mother can also be small for gestational age or born with a normal birth weight [35, 36]. Of particular note, being small or large for gestational age due to maternal obesity predispose the offspring to obesity in adulthood [9]. Several animal studies have investigated the relationship between maternal obesity and the development of obesity in the offspring [37–39]. In rats, exposure to maternal obesity during pregnancy and lactation increased the risk of obesity later in life [37, 38]. The risk of obesity was further exacerbated when the offspring consumed a high fat diet postweaning [37, 40]. These clearly indicate that maternal obesity increased the obesity risk in their offspring. There are a number of mechanisms that may explain the programming effects of maternal obesity on offspring obesity risk including programing of appetite dysregulation and altered adipogenesis.

A study reported that the offspring of mice that consumed a high fat diet throughout pregnancy and lactation were hyperphagic from 4 to 6 wk of age before they developed abdominal obesity at 3 months [39]. Similarly, offspring of rats exposed to a junk food diet during both pregnancy and lactation displayed an increased preference for fatty, sugary, and salty foods when compared to offspring exposed to a control diet [37]. Programed changes in the offspring
of obese mothers may be a consequence of changes in hypothalamic functioning, which has an important role in the regulation of appetite. Appetite is primarily regulated by the hypothalamic arcuate nucleus and is composed of two neuron populations that either express the appetite stimulator neuropeptide Y (NPY) or the appetite inhibitor pro-opiomelanocortin (POMC) [41]. These neurons project into the paraventricular nucleus where they exert their effect on appetite regulation [41]. Importantly, the development of appetite regulation occurs during late gestation and perturbations during these critical periods may lead to a dysregulation in the expression of hypothalamic neuropeptides, increasing the risk of obesity in adulthood [41]. In rats, offspring of dams exposed to a cafeteria diet during pregnancy and lactation have increased hypothalamic NPY signaling [42]. Additionally, offspring born from genetically obese Zucker rats had reduced expression of POMC and lower α-melanocyte stimulating hormone, a cleaved product of POMC [43]. It is suggested that the changes in these neuronal pathways may be due to increased circulating leptin and insulin in the obese state, which are known to play a major role in regulating appetite by stimulating POMC and inhibiting NPY hypothalamic neurons [44, 45]. Therefore, it is postulated that exposure to maternal obesity causes alterations in hypothalamic regulation of appetite in the offspring leading to the development of hyperphagia.

Maternal obesity is also associated with dysfunction in offspring adipose tissue development. Offspring of rat dams fed a “junk food” diet during gestation and lactation demonstrated adipocyte hypertrophy, independent of hyperplasia, with increased expression of adipogenic factor peroxisome proliferator-activated receptor gamma, insulin-like growth factor 1, insulin receptor substrate 1, and vascular endothelial growth factor A mRNA expression at 10 wk of age, indicative of altered adipocyte proliferation [46]. Similarly, maternal overnutrition during late gestation in sheep is also associated with increased expression of genes, which regulate adipogenesis and lipogenesis in fetal perirenal adipose tissue, including lipoprotein lipase, adiponectin, leptin, and peroxisome proliferator-activated receptor gamma [47]. These findings suggest that alterations in adipose gene expression may be one of the underlying mechanisms that increase adiposity in offspring that are exposed to maternal overnutrition.

In addition to increasing the risk of offspring obesity, maternal obesity and overnutrition also program metabolic dysfunction in their offspring. Limited human studies have examined the link between maternal obesity, offspring insulin resistance, and other adverse metabolic outcomes. For instance, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reported that an increase in maternal BMI is linked with fetal hyperinsulinemia, which is independent of maternal glycaemia [48]. Importantly, there is evidence that demonstrates that babies of obese mothers develop insulin resistance in utero, indicating that maternal obesity is an important predictor of metabolic disease in their offspring [49]. The effect maternal obesity has on insulin sensi-
whereas maternal malnutrition is the main cause of babies born small in developing countries [67,68]. Previous epidemiological studies have demonstrated an association between being born small and an increased risk of developing type 2 diabetes, obesity, and hypertension [5,6,69]. From these findings the importance of maternal nutrition and its effect on birth weight and subsequent adult diseases was addressed in human studies of famine exposure, particularly the Dutch Hunger Winter of 1944–1945 [70,71]. The Dutch Hunger Winter study found that growth restriction due to famine exposure in utero is linked to glucose intolerance and abdominal obesity in adults [70,72]. In contrast, the findings from famine exposure during the Leningrad siege (1941–1944) did not show any association between birth weight and metabolic disease risk [73]. The inconsistency between these findings is likely due to the different nutritional environments during the postnatal period in both studies. Following the Dutch Hunger Winter, the food supply was restored to normal levels in a short period of time, where they were exposed to normal nutrition during their postnatal life [70,73]. Conversely in Leningrad, the children were exposed to poor nutritional environment in utero and in their early postnatal years [73]. These findings suggest that a mismatch in nutritional environment between the intrauterine and postnatal period may influence the outcomes of growth-restricted babies in adulthood.

Altered postnatal growth can also influence the disease outcomes of growth-restricted babies in adulthood. Growth-restricted babies often experience catch up growth in the first 6 to 12 months of age and to as late as 2 years after birth when the postnatal nutritional environment is improved [74]. They will accelerate their growth trajectory to match the growth of normal weight babies to compensate for their low birth weight. Previous studies have reported that children born small for gestational age, who have a high childhood fat mass, have an increased risk of developing diabetes in later life [75,76] and present with insulin resistance at 3 years [77]. Another study in a cohort from Helsinki demonstrated that growth-restricted individuals have an exacerbated risk of type 2 diabetes when catch up growth in early postnatal life (6 months of age) is combined with accelerated weight gain during adolescence [78]. These studies suggest that accelerated catch up growth during postnatal life is an additional independent risk factor to disease development in growth-restricted individuals. Therefore, a combination of adverse pre- and postnatal environment can lead to an exacerbation of the programmed diseases in these individuals.

Animal models have been extensively used to identify the underlying mechanisms that associate intrauterine growth restriction and the risk of metabolic dysfunction in adulthood. Indeed, many studies using a wide range of animal species, including sheep, rodents and guinea pig, have demonstrated the link between intrauterine growth restriction and metabolic disease [79]. The majority of animal models investigating intrauterine growth restriction have utilized dietary interventions to induce maternal undernutrition [80,81] and surgical interventions to induce uteroplacental insufficiency [82]. In Wistar rat, exposure to 50% caloric restriction in the last trimester of pregnancy resulted in a 16% reduction in birth weight compared to control offspring [83,84]. However, the effect caloric restriction has on adiposity is contradictory with this study identifying no change [83,84], whereas another study identified increased adiposity, which is consistent with the hyperleptinemia observed in these animals [85]. Despite these differences in adiposity, caloric restriction results in catch up growth [86] and alters β-cell morphology and function [83,84]. Specifically, caloric restriction and low-protein diets (8% protein) reduce β-cell mass [83,87–89] and insulin content [83,87]. Interestingly, when these offspring were exposed to a normal diet postnatally, the islet morphology improved, indicating that the in utero environment influences fetal islet development [88,89]. However, if protein restriction was extended during weaning, these modifications were irreversible [88,89]. Studies in male rat offspring of low-protein diet dams demonstrated an age-dependent loss in glucose tolerance. Specifically, they had improved glucose tolerance and reduced plasma insulin concentrations in early life (6 wk to 3 months), which is indicative of enhanced insulin sensitivity [90]. Nevertheless, when they reached 15 months of age, glucose intolerance was evident [91] and by 17 months of age they developed frank diabetes and insulin resistance [92].

As mentioned previously in developed countries, placental insufficiency is the major cause of intrauterine growth restriction and low birth weight [64–66]. Wigglesworth was the first to describe the model of uteroplacental insufficiency in rats by ligating the uterine vessels during late gestation, which reduced uteroplacental nutrient and oxygen perfusion and thus compromises fetal growth and development [82]. This rat model is equivalent to the degree of birth weight reduction observed in humans in developed countries (10–15% reduction in birth weight), where developmental insults are most apparent during late gestation [93]. Uteroplacental insufficiency surgery in Sprague Dawley rats between embryonic days 16 and 19 (E16-19; term = 22 days) resulted in low birth weight offspring (10–15%) [64,94,95]. These offspring had reductions in β-cell mass at birth [95,96], with a similar decrease in pancreatic insulin content [95], however, glucose tolerance was normal at 3 months of age [95]. In contrast, a study by Simmons et al. reported that male growth-restricted Sprague Dawley rats had normal β-cell mass, islet size, and pancreatic weight at 1 and 7 wk of age [64]. However, at 15 wk of age, these rats had reduced β-cell mass and decreased pancreatic insulin content as well as a reduced insulin response to glucose, and at 26 wk these offspring were diabetic and obese [64]. Additionally, other uteroplacental insufficiency studies recorded fasting hyperglycemia, early onset insulin resistance, obesity, and impaired glucose tolerance in the growth-restricted Sprague Dawley rats [64,65,97–100]. Findings from our laboratory reported that male Wistar Kyoto (WKY) rats that were exposed to uteroplacental insufficiency develop impaired glucose tolerance and were
hyperinsulinemic at 6 month of age, which was associated with a 40–45% reduction in β-cell mass [101–104]. Interestingly, growth-restricted female rats exhibited normal glucose tolerance regardless of reductions in basal insulin concentrations and pancreatic β-cell mass [101, 105]. Findings from these studies clearly suggest that there are sex-specific differences where growth-restricted males are more severely affected than females. Thus, “second hits,” such as obesity or pregnancy, may exacerbate the adverse metabolic phenotype in growth-restricted females.

4.1 Growth restriction and obesity

Epidemiological studies and animal models link a low birth weight to an increased risk of adult obesity and metabolic syndrome [106, 107]. Early epidemiologic studies demonstrated that growth-restricted babies that experienced accelerated catch up growth have a higher risk of obesity and metabolic syndrome compared to infants that are born small and remain small throughout their life [108, 109]. Importantly, growth-restricted infants with catch up growth during their early postnatal life had reduced lean body mass and elevated abdominal fat [110, 111]. This finding is similar to what is reported in infants with a normal birth weight that exhibit rapid weight gain in the first 2 years of life [112]. Of particular concern, the Dutch Hunger Winter study reported that only women who were exposed to famine in early gestation had increased in body weight, BMI, and waist circumference in adulthood [72]. Likewise, girls aged between 14 and 16 years who were born small had increased central adiposity compared to growth-restricted males [113]. These findings indicate that growth-restricted females are at higher risk of abdominal obesity which is associated with an increased risk of insulin resistance and glucose intolerance.

4.2 Growth restriction and pregnancy

In females that were born growth-restricted, pregnancy may exacerbate their risk of cardiovascular and metabolic disease due to an increase in both maternal and fetal demands. Indeed, epidemiological studies associate a low birth weight with a higher risk of developing preeclampsia during later pregnancy [114, 115]. Furthermore, women born with a low birth weight were also more susceptible to gestational diabetes during pregnancy compared to women that were born of normal weight [116]. A study in female rats born small also identified a higher risk of developing gestational diabetes in pregnancy as well as an increased risk of their offspring developing an altered metabolic phenotype [94]. Likewise, we have previously demonstrated that growth-restricted female rats during late pregnancy develop glucose intolerance, despite a normal plasma insulin response [105]. Given that maternal obesity has adverse effects on glucose homeostasis during pregnancy, it is likely that the metabolic dysfunction in pregnant females who were born growth-restricted will be exacerbated if they consume a high-fat diet. Currently this association has not been investigated, thus future studies should examine this interaction.

So far, most of the developmental programing studies are largely descriptive and there are very limited molecular investigations have been performed in this area. Therefore, additional molecular studies are required to identify the underlying mechanisms that may explain the link of obesity in growth-restricted mothers to their pregnancy outcomes as well as their offspring development.

5 Potential intervention

There has been much interest in the development of lifestyle interventions targeting overweight and obese pregnant women. Of particular interest, epidemiological studies demonstrated that exercise in overweight and obese women prevented them from developing gestational diabetes as well as delivering macrosomic babies [117]. Moderate exercise during pregnancy improved glucose tolerance [118] and reduced fasting insulin [119] in obese pregnant women; thus, lowering their risk for gestational diabetes. Likewise, moderate to vigorous exercise in early pregnancy also improved insulin response and sensitivity, as well as reducing plasma triglyceride concentration in overweight and obese pregnant women [120]. However, there are studies that failed to associate the beneficial effects of exercise with a reduced risk of adverse pregnancy outcomes in overweight and obese women [121, 122]. Lack of consistent evidence regarding the benefits of exercise in pregnant obese or overweight women suggests that interventions during pregnancy alone may not be enough to ameliorate the adverse effect obesity has on the mother and her children. Therefore, an exercise intervention before and during pregnancy may be more beneficial. Indeed, in nonobese pregnant women who were involved in exercise training 1 year before pregnancy had a reduced risk of developing gestational diabetes [123–125], and the effect was greater in women who exercised before and during pregnancy [125]. These findings propose that these lifestyle interventions are more beneficial if they are performed before the reproductive years.

Similarly, in animal studies, maternal exercise reduced the metabolic risk caused by maternal obesity in both the mother and offspring [126, 127]. A recent study on rats reported that voluntary wheel running before and during pregnancy prevented the increase in plasma insulin and glucose, concentrations insulin resistance (HOMA-IR), and plasma triglyceride content during lactation in obese dams [126]. Additionally, voluntary exercise before and during pregnancy reduced glucose and insulin concentrations in male offspring (postnatal day 19) of obese rat mothers [128] and prevented glucose intolerance induced by maternal obesity in female offspring (24 wk) of C57BL/6 mice [128]. Of particular concern, most of the rodent studies investigating the effect of
exercise intervention in maternal obesity utilized a poorly con-
trolled voluntary wheel running as the exercise intervention. Therefore, a well-controlled interventional animal study us-
ing a motorized treadmill exercise is required as precise ex-
ercise intensity and duration can be controlled.

6 Conclusions

There has been a significant increase in the number of over-
weight or obese pregnant women in the past two decades. Of
particular concern, maternal obesity does not only affect the
mother, but the offspring are programed to develop obesity
and metabolic disease later in life. Studies suggest that the
mechanisms contributing to this is due to appetite dysreg-
ulation and enhanced adipogenesis in the offspring. Being
born small for gestational age is one of the risk factor for
developing obesity. As being born small is associated with
increased risk of cardiovascular and metabolic disease dur-
ing pregnancy, it is suggested that obesity during pregnancy
may exacerbate the risk of these diseases. However, there are
limited studies investigating the effect of maternal obesity in
growth-restricted mothers and the subsequent effects in their
offspring. Therefore, it is critical to identify the underlying
mechanisms that link obesity in growth-restricted mothers
to the development of metabolic diseases in their offspring.
This will be fundamental to future strategies for the preven-
tion and therapy of obesity.

The authors have declared no conflicts of interest.

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