Maternal Obesity, Metabolic Health, and Prenatal Programming of Offspring Obesity

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Abstract: Children born to overweight and obese women, as compared to those of normal weight women, have greater risk for becoming obese themselves and suffering comorbid metabolic health problems. Evidence is accumulating that this increased susceptibility is at least partially attributed to a prenatal programming effect, whereby obesogenic factors in the intrauterine environment alter fetal development of systems involved in body weight regulation thereby promoting deposition of excess adipose tissue. There is little evidence that maternal adipose tissue in and of itself is involved in programming the developing fetus toward obesity; rather, maternal obesity increases risk for metabolic health perturbations during pregnancy and it is these perturbations that appear to be involved in programming offspring risk for obesity. The considerable variability in the metabolic health of individuals, even among those of the same body mass index (BMI), highlights the fact that maternal BMI lacks precision for the identification of pregnancies that will convey increased risk of obesity to offspring. The purpose of the following review is to discuss evidence that maternal metabolic health is involved in the prenatal programming of obesity, and to identify simple maternal markers related to metabolic health, that may increase precision in the identification of obesogenic pregnancies.

Keywords: BMI, adiposity, metabolic health, gestational diabetes, hypertension, inflammation, dyslipidemia, waist circumference, family history, recent weight gain.

INTRODUCTION

Rates of childhood obesity in the United States continue to rise despite increased public health awareness. National Health and Nutrition Examination Survey (NHANES) data collected in 2003-4 found that the prevalence of overweight and at risk for overweight was 26% among children aged 2-5 year and 37% among children aged 6-11 years; representing a 20-25% increase in prevalence since 1999 [1]. Given the relative ineffectiveness of weight loss and weight loss maintenance interventions, the best “treatment” for obesity is likely to be primary prevention. In recent years, strong evidence in support of prenatal programming of offspring obesity has accrued, whereby factors related to maternal health are believed to alter fetal development in utero in a manner that promotes excess adipose tissue deposition during pre- or post-natal life. Thus, the optimal time to prevent childhood obesity may be during pregnancy itself. But, how do we pre-determine which children may benefit from an intervention provided to mothers during pregnancy? Certainly, evidence suggests that children of women who begin pregnancy in an overweight or obese state are at greater risk for becoming obese themselves, but there is little evidence that maternal adipose tissue itself directly contributes to the prenatal programming of obesity. Rather, excess adiposity among women increases the risk for other metabolic health abnormalities during pregnancy, and it is those abnormalities that appear more likely to contribute to offspring obesity risk. But considerable variability exists in terms of metabolic health among people of any given weight. Therefore, maternal weight lacks precision as an identifier of risk for providing an obesogenic intrauterine environment to offspring.

The purpose of this review is to examine what is known about associations between maternal BMI status and metabolic health abnormalities, and their potential effect on prenatal programming of obesity among offspring. We will briefly review the literature regarding associations between maternal and offspring obesity, then discuss evidence for the involvement of maternal obesity-related metabolic abnormalities in the prenatal programming of obesity. Finally, we will discuss potential identifiers of pregnancies that carry increased risk for providing an obesogenic environment. Although many other reviews have been written regarding the consequences of maternal obesity during pregnancy, to our knowledge, none has focused on the topic of refining the identification of pregnancies that are likely to convey increased obesity risk to offspring. This discussion is not intended to be an exhaustive review of the literature, but rather aims to stimulate thought regarding how we might achieve the earliest and most precise identification of children who are at risk for prenatal programming of obesity, at a time when prevention may be possible.

ASSOCIATIONS BETWEEN MATERNAL OBESITY AND OFFSPRING RISK FOR OBESITY

Numerous studies have shown a relationship between exposure to maternal obesity in utero and offspring obesity at various ages. In a meta-analysis of published studies, Chu et al. [2] found that the prevalence of macrosomia among
neonates of obese women was almost double that of those born to women of normal weight. Although across a range of birth weights, increased birth weight is not associated with increased adiposity [3], those at the extreme upper end of birth weights have greater fat mass than those born of appropriate size for gestational age [4, 5]. Beyond birth, infants and children born to women who were overweight prior to or early in pregnancy have greater BMI and more adiposity than children born to women of normal weight [6-12]. Finally, children born to overweight women have increased risk of indices associated with metabolic syndrome such as insulin resistance and dyslipidemia [7, 13, 14]. Although these studies are observational and as such, cannot imply causation, the consistency of these findings lends credence to the hypothesis that intrauterine exposure to maternal obesity predisposes offspring toward the development of obesity and impaired metabolic health.

Studies investigating modifications in maternal weight prior to conception have provided more support for a causal relationship between maternal and offspring birth weight or obesity. In consecutive pregnancies, women with increases in pre-pregnancy BMI from normal to obese between the first and second pregnancies had significantly increased risk for delivering a large-for-gestational-age (LGA) neonate, whereas in women with a decrease in pre-pregnancy BMI, risk of LGA was attenuated compared to those who maintained a higher BMI in the second pregnancy [15]. In a study of children born prior to or after their mothers’ weight loss surgery, Kral et al. [16] showed that the prevalence of obesity among children born post surgery was similar to that of the general population (~35%), whereas the prevalence among children born prior to mothers’ weight loss surgery was significantly greater (60%). Interestingly, this effect was observed despite the fact that the mothers were matched for BMI at the time of conception, suggesting that a mechanism other than that related to absolute amount of maternal adiposity increases risk of obesity among offspring. A comparable effect has been shown among Pima Indians who have a very high prevalence of type 2 diabetes, wherein children born prior to a maternal diagnosis of type 2 diabetes were less likely to become obese and diabetic themselves as compared to their siblings who were born following the development of maternal diabetes [17]. Data from animal models also support a causal effect of maternal obesity on offspring adiposity [18-20]. In an interesting study of offspring from obesity-prone dams who were permitted to become obese versus those who remained lean, pups from obese dams had greater adiposity than pups from the lean but obesity-prone dams [18]. These data suggest that despite a similar genotypic predisposition for obesity, differences in the intrauterine environment explain variance in offspring presentation of obesity.

The mechanisms underlying the interrelationships between maternal obesity and offspring adiposity and metabolic health are yet to be clearly elucidated. There is little evidence that the observed association between maternal and offspring obesity is due to excess maternal adiposity itself. Rather, a significant portion of the risk to offspring of women who were overweight during pregnancy is believed to be attributable to the influence of obesity-induced abnormalities in maternal metabolic health on prenatal programming of fetal body composition and metabolism.

MATERNAL METABOLIC FACTORS RELATED TO PRENATAL PROGRAMMING OF OBESITY

The hypothesis that the prenatal environment predisposes individuals to certain phenotypes [21, 22] has been gaining support in recent years. Pertinent to this review, obesity in the mother is hypothesized to alter her metabolism in a manner that supports an “obesogenic” intrauterine environment; providing excess nutrient supply to the developing fetus, and thereby programming altered fetal metabolism that promotes adipose tissue deposition [23, 24]. Although evidence supporting this hypothesis has accumulated, the obesity-induced changes in maternal metabolism that impact fetal development have not been fully elucidated.

Excess adiposity is commonly associated with abnormal metabolic health such as impaired glucose tolerance, dyslipidemia, hypertension and inflammation. Among non-pregnant adults, clustering of these symptoms determines the presence of the metabolic syndrome and is predictive of future cardiovascular disease and type 2 diabetes. A study from Ramsay et al. [25] showed that these metabolic perturbations are more common among obese versus lean pregnant women, and are sustained throughout pregnancy. Furthermore, due to the increased metabolic demands of pregnancy, subtle deficits in metabolic health may initially only be identified during pregnancy and resolved following pregnancy, at least until such time as other factors such as age or adiposity facilitate progression to a clinically recognized disorder. Indeed, studies have shown that women with a history of gestational diabetes and hypertensive disorders during pregnancy are more likely to develop components of metabolic syndrome in later life [26-29]. Consequently, metabolic abnormalities presenting during pregnancy may be indicative of subtle underlying impairments in women that not only predict her future health, but also, as discussed below, may directly influence obesity risk in offspring.

Impaired Glucose Tolerance

By far, the greatest amount of research regarding maternal metabolic health and offspring obesity has centered on the effect of impaired maternal glucose tolerance. Maternal insulin resistance serves a functional purpose during pregnancy in that it increases delivery of glucose to the fetus, facilitating fetal growth. Among healthy women, greater insulin release will counteract this insulin resistance so that maternal glucose concentrations remain within a tight range. If, however, the compensatory insulin response is not sufficient, maternal glucose concentrations will be relatively high and fetal overgrowth may occur. Women who are overweight and obese prior to, or early in, pregnancy are more likely to have reduced insulin sensitivity [24] and insufficient compensation for that reduced sensitivity, resulting in gestational diabetes [2, 30]. Furthermore, although impaired glucose tolerance is more likely to occur in women who are overweight or obese, any subtle deficits of glucose metabolism among women of normal weight may initially present themselves during pregnancy because of changes in metabolic demands.

The effect of gestational diabetes on offspring obesity has been extensively studied. In the 1950’s, Pedersen’s observation that infants of diabetic mothers were heavier
than those of non-diabetic controls led him to hypothesize that maternal hyperglycemia among diabetic women resulted in fetal hyperinsulinemia which, in turn, was associated with greater deposition of fat [22]. More recent research has supported this hypothesis by showing that infants born to women with pre-existing or gestational diabetes are larger [31, 32] and have greater adiposity at birth [33]. It is now apparent that even mild, subclinical, elevations in maternal glucose are associated with increased neonatal birth weight and adiposity [34-36]. Beyond birth, children born to women with gestational diabetes continue to be at greater risk for obesity and comorbid metabolic health problems [7, 32, 37-40]. Thus, intrauterine exposure to relatively high levels of maternal glucose, which is more likely to occur among children of obese women, increases the risk for excess adipose deposition both during prenatal development and during childhood.

Although the mechanism underlying maternal diabetes-related prenatal programming of offspring obesity has not been definitively shown, it is believed to be consistent with Pedersen’s hypothesis and is outlined in Fig. (1). Elevated insulin and C-peptide (indicative of increased insulin secretion) concentrations have been found in amniotic fluid and cord blood of fetuses of women with gestational diabetes [36, 41, 42]. Regardless of whether the fetal hyperinsulinemia is due to insulin resistance or increased insulin secretion, the insulin is believed to facilitate deposition of excess adipose tissue. Fetal insulin has been associated with subsequent adiposity in childhood and beyond [31, 43]. In addition to the potential for altered programming of the fetal pancreas during development, excess insulin may also affect programming of the hypothalamus, thereby influencing the regulation of satiety and energy balance (for review see [44, 45]). Therefore, intrauterine exposure to elevated maternal glucose is hypothesized to increase fetal insulin concentrations, which in turn may alter prenatal programming of multiple systems important for body weight regulation.

Although obesity and increased maternal glucose concentrations adversely modify offspring risk for obesity, the risk can be attenuated with appropriate intervention. Adequate treatment of gestational diabetes, or even of mild hyperglycemia, has been shown to reduce birth weight and attenuate the risk for obesity among offspring [46-49]. This raises the tantalizing possibility that prenatal programming of obesity by maternal hyperglycemia is modifiable with an appropriate intervention to facilitate maternal glycemic control. Importantly however, it is essential that high-risk pregnancies be identified, even if they don’t meet the clinical cut-points for diabetes, in order to appropriately target intervention efforts.

We must also acknowledge that even with successful intervention aimed to achieve optimal control of maternal gestational glucose concentrations, prenatal programming of obesity may still occur. A number of studies have shown an effect of maternal obesity on offspring birth weight and adiposity that is independent of maternal diabetes status [50-52]. Although some of this risk may be attributed to an effect

![Fig. (1). Hypothesized role for maternal impaired glucose tolerance in the prenatal programming of fetal systems involved in the regulation of energy balance; ultimately predisposing offspring toward the development of obesity.](image-url)
of subclinical elevations in maternal glucose among non-diabetic obese women, it is possible that other obesity-induced abnormalities in metabolic health, such as hypertension, hyperlipidemia, and inflammation, also play a role in prenatal programming.

**Hypertensive Disorders of Pregnancy**

Pre-pregnancy overweight and obesity is associated with increased systolic and diastolic blood pressure during each trimester of pregnancy compared to that of lean women [53]. It is not surprising therefore, that pregnancy-induced hypertension and preeclampsia are more prevalent among women who are overweight or obese prior to or during pregnancy [54-56]. Hypertension during pregnancy has consistently been related to fetal intrauterine growth restriction (IUGR) presumably due to compromised nutrient delivery to the fetus, and IUGR itself places children at risk for subsequent obesity due to excess adipose deposition during a period of catch-up growth. At the other end of the spectrum however, only a few studies have shown an effect of pregnancy hypertensive disorders on fetal overgrowth and the prevalence of delivering an LGA infant [57, 58]. While one study showed that this effect was maintained after adjustment for maternal BMI [57], the other did not [58]. Therefore, it is unclear whether hypertensive disorders of pregnancy, in and of themselves, contribute to the prenatal programming of obesity. If a role for maternal hypertension in prenatal programming of obesity exists, a potential mechanism by which this might occur has not been elucidated.

**Maternal Lipid Concentrations**

Total cholesterol, high-density lipoprotein – cholesterol (HDL-C), and triglyceride levels increase in normal pregnancy as compared to those of non-pregnant women [59-61]. In comparison to lean pregnant women, obese pregnant women have higher triglyceride and lower HDL-C concentrations [25]. Elevated cholesterol and triglycerides either prior to or during pregnancy are associated with increased risk of complications during pregnancy such as preeclampsia [55], glucose intolerance and gestational diabetes [60, 62, 63]. In terms of offspring outcomes, high maternal triglyceride concentration during pregnancy is associated with increased birth weight, independently of maternal BMI [61-65]. In a study of women with well-controlled gestational diabetes, maternal free fatty acids (FFA) and triglyceride concentrations were positively associated with fetal abdominal circumference during the 3rd trimester, and those measured close to delivery were positively associated with levels measured in cord blood and with risk of delivering an LGA infant [65]. Furthermore, elevated maternal triglyceride concentration among this group of women was associated with increased neonatal fat mass. To our knowledge, no other study has shown an association between maternal triglyceride or lipid concentrations during gestation and subsequent childhood adiposity among offspring.

While maternal triglyceride does not cross the placenta, the presence of high triglyceride concentrations during late gestation provides a source for FFA, which are essential for fetal growth. Therefore, a mechanism exists whereby maternal lipids could impact fetal growth and potentially predispose offspring to obesity. More research is needed however, to understand whether perturbations of maternal lipids contribute to increased adiposity in childhood or beyond, and whether the effect of exposure to elevated maternal triglyceride and FFA on neonatal birth weight and adiposity is independent of any other disorders of maternal metabolic health.

**Maternal Inflammation**

Obesity has been described as a subclinical inflammatory condition due to the elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6) found in overweight and obese adults and children [66, 67]. Increased concentrations of inflammatory markers are associated with future risk for adverse cardiovascular events [68] and for the development of type 2 diabetes [69]. Given these results of general population studies, it is not surprising that women who are obese prior to or early in pregnancy have increased CRP and IL-6 concentrations [25, 70, 71]. Furthermore, maternal CRP is associated with adverse pregnancy-related problems such as preeclampsia [72], and gestational diabetes [71, 73]. In terms of offspring outcomes, one study using an animal model found that offspring of dams administered exogenous IL-6 during pregnancy had more adipose tissue and that male offspring specifically, were more insulin resistant than those from dams not given exogenous IL-6 [74]. To our knowledge, only one clinical study has shown an association between maternal inflammation and offspring obesity, with neonatal adiposity being positively associated with maternal IL-6 concentration [75].

Investigations of placental transfer of IL-6 and other inflammatory cytokines have yielded conflicting results [76, 77], so the potential for maternal inflammation to directly influence offspring birth weight or adiposity is unclear. There is evidence, however, that offspring of obese women have increased inflammation themselves. In a comparison of lean versus obese mothers, Catalano et al. [78] showed that fetal cord blood of neonates born to obese women had higher levels of IL-6 than did that of neonates born to lean mothers, although it was not clear whether this association was related to the increased size of the neonates born to obese women. A study of neonates born to women with type 1 diabetes found that although birth weight was unrelated to IL-6 and CRP concentrations in cord blood, leptin, which corresponds to fetal adiposity, was positively associated with cord blood IL-6 and CRP [79]. Thus, while data from clinical studies does not, at this time, support a direct association between the intrauterine exposure to maternal inflammation and fetal overgrowth or prenatal programming of obesity risk, offspring themselves may be at increased risk for being born in a subclinical inflammatory state if they have more adiposity at birth.

Taken together, research indicates that metabolic health abnormalities, rather than frank obesity per se, may explain the increased risk for obesity among children of overweight and obese women. Evidence supports the potential for maternal hyperglycemia due to glucose intolerance, and possibly high maternal triglyceride and FFA concentrations, to directly impact fetal growth and prenatal programming of obesity. Despite the lack of evidence for a direct effect of maternal hypertension or inflammation on offspring adipo-
sity, their association with other metabolic abnormalities, such as diabetes [71, 73, 80-83], may render them useful indices for the identification of pregnancies that are more likely to provide an obesogenic intrauterine environment. Although we limited our discussion above to maternal indices associated with the metabolic syndrome, there are likely other maternal metabolic perturbations, such as increased glucocorticoid concentrations [84], that are associated with increased adiposity among offspring. More research is needed to characterize all metabolic abnormalities associated with excess adiposity during pregnancy, and to understand potential mechanisms whereby any abnormalities could influence fetal development. Furthermore, given the unique metabolic challenge pregnancy provides, the disease-risk cut-points that are appropriate for the non-pregnant population may not be applicable for the determination of offspring obesity risk. It is important to work toward developing cut-points specific to pregnancy that portray increased risk for adiposity among offspring.

HOW CAN WE IMPROVE THE IDENTIFICATION OF PREGNANCIES WITH INCREASED RISK FOR PRENATAL PROGRAMMING OF OBESITY?

One of the underlying assumptions of the hypothesis relating maternal obesity to prenatal programming of obesity is that excess adiposity adversely affects metabolism in the mother. Certainly obesity increases risk for impaired metabolic health, but considerable heterogeneity among obese people exists in terms of the presence and severity of related components related. While two people could share a common BMI, irrespective of whether it is in the lean or obese range, one might present with impairments in metabolic health while the other may not. These differences in metabolic health could potentially result in different prenatal environments, which ultimately may contribute to differences in offspring obesity risk (Fig. 2). The complexity of variation in metabolic health at any given weight class among the non-pregnant population was first acknowledged in the 1980’s [85-87], and has recently been reviewed [88-91]. The implied message from these studies is that weight status is merely one component associated with metabolic health, but does not identify the actual presence of any metabolic abnormalities.

Similarly, given the data described above regarding the effects of various metabolic health abnormalities on offspring risk for obesity, it is our contention that maternal BMI during early pregnancy is not specific enough to adequately identify pregnancies that are likely to provide an obesogenic intrauterine environment. Among the non-pregnant population, it is estimated that approximately 12-20% of overweight and obese people lack any components

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**Fig. (2).** Hypothesized associations between maternal weight status, maternal metabolic health, and offspring risk for obesity. There is more evidence that perturbations of maternal metabolic health, rather than maternal obesity per se, are directly associated with prenatal programming of obesity. The considerable variability in metabolic health among women of any specific weight however, implies that maternal weight status itself lacks precision for the identification of high risk pregnancies. The gray box denotes maternal markers, independent of simple BMI status, that may be associated with perturbations of maternal metabolic health and thus more likely to identify pregnancies with higher risk for providing an obesogenic intrauterine environment for offspring. Dashed arrows and box denote potential mediators of the relationship between prenatal programming of obesity and subsequent childhood obesity that are not addressed in this review.
of the metabolic syndrome [89, 92]. A comparable portion of women who enter pregnancy in an overweight or obese state may be otherwise metabolically healthy and thus pose no greater risk for providing an obesogenic environment to their fetuses than do women who are normal weight early in pregnancy. Conversely, a significant proportion of people with BMI in the normal range are likely to have one or more components of the metabolic syndrome, potentially placing their children at risk for subsequent obesity. If assessment of offspring risk for obesity were based solely on maternal BMI status, normal weight women with subtle metabolic abnormalities would be overlooked. Research is needed to determine whether women who are obese but otherwise free of any metabolic abnormalities convey any increased risk for obesity, in utero, to their offspring, and comparatively, whether women of normal weight who present with subtle underlying metabolic abnormalities increase the risk of obesity among their offspring. Furthermore, we need to identify reliable markers that are easily obtained in a clinical setting, in addition to weight status, that infer the potential for impaired maternal metabolic health during pregnancy and subsequent risk of offspring obesity.

To address this last point, Sims [90] suggested diagnostic criteria that are associated with metabolic health among obese non-pregnant people. Specifically, despite being overweight or obese, people who might be protected from obesity-related metabolic perturbations are those with normal insulin resistance, those with widely dispersed adiposity (as opposed to a greater proportion of central adiposity), and those who have family members with early-onset obesity who are relatively free of components associated with the metabolic syndrome. Furthermore, Muscelli et al. [93] and Brochu et al. [94] found that obese people were less likely to be afflicted with components of the metabolic syndrome if they had been obese for a relatively long duration, or if the age of obesity onset was younger than 20 years of age. It is not known whether individuals with relatively early onset obesity are fully protected from impairments of metabolic health, or whether they have a different threshold for mediating factors such as age or adiposity, beyond which metabolic perturbations arise.

Some studies have shown the capacity of these indices to predict maternal metabolic health abnormalities during pregnancy. Specifically, increased maternal waist circumference during early pregnancy, which serves as a proxy index of visceral adiposity [95], has been associated with increased risk for the development of gestational hypertension and preeclampsia [96], and with gestational glucose intolerance [97]. Relatively higher fasting and 2hr insulin response during an oral glucose challenge prior to 16 weeks gestation is predictive of increased risk for gestational diabetes among women with at least one other risk factor, such as obesity [98]. A family history of preeclampsia or diabetes has been associated with increased risk for preeclampsia and gestational diabetes, respectively [99-101]. Interestingly, there is some evidence that a history of diabetes among maternal relatives conveys greater risk for gestational diabetes than does a similar history among paternal relatives [101]. Hence, prenatal programming of obesity and diabetes risk may well be a self-promoting cycle whereby impaired glucose toler-
ABBREVIATIONS

BMI = Body mass index
LGA = Large-for-gestational-age
IUGR = Intrauterine growth restriction
HDL-C = High-density lipoprotein - cholesterol
FFA = Free fatty acids
IL-6 = Interleukin-6
CRP = C-Reactive protein

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The Open Obesity Journal, 2011, Volume 3


The Open Obesity Journal, 2011, Volume 3

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Received: August 22, 2009 Revised: September 22, 2009 Accepted: October 30, 2009

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