The Association between Maternal Obesity and Neurodevelopmental Outcomes of Offspring

Shobha H. Mehta, MD[1], Jean M. Kerver, PhD, MSc, RD[2], Robert J. Sokol, MD[3], Daniel P. Keating, PhD[4], and Nigel Paneth, MD, MPH[2,5]

The prevalence of obesity has doubled worldwide since 1980, and the World Health Organization estimates that over 1.4 billion people around the world are obese.[1] In the US, it is estimated that 36% of all adults and 32% of all reproductive-age women (age 20-39 years) now have a body mass index (BMI) greater than 30 kg/m^2, the most widely used definition of obesity.[2] The impact of obesity on human health has been well chronicled, including increases in cardiovascular disease, hypertension, type 2 diabetes, cancer, and degenerative joint disease.[3,4] Concern has been expressed that the increase in obesity and its resultant morbidities could lead to the first sustained drop in life expectancy in the US in the modern era.[5]

In recent years, the transgenerational effects of obesity have becoming increasingly emphasized. Many studies have shown an association between maternal prepregnancy obesity and/or excessive weight gain during pregnancy and adiposity of the offspring, including gestational overgrowth[6,7] and child and adult obesity.[8,9] Findings consistent with metabolic syndrome in young children have also been seen following these exposures.[10] A small but growing literature focuses on the relationship between maternal obesity (ie, obesity in the mother noted at the beginning of pregnancy or before) and neurodevelopment of the offspring. Four outcomes will be addressed—cerebral palsy (CP), autism, cognitive impairment, and behavioral/psychiatric disorders, and we will examine the mechanisms that may link these findings to maternal obesity.

What Is Obesity?

The attention paid to obesity in the medical literature has not always been accompanied by consideration of what the concept represents and how it should be assessed.

What Is the Best Measure of Obesity?

The first problem is that the usual working definition of obesity does not directly assess the core concept in obesity, which is excessive fat deposition. The difficulties involved in quantifying adipose tissue directly have led most population investigators to substitute BMI–weight/height^2, for excessive adiposity, and to use a BMI $\geq$30 kg/m^2 as the point above which individuals are described as obese. Although a very large fraction of the obese, as defined by BMI, has excessive fat deposition, field studies would be stronger if BMI were partitioned into fat mass and fat-free or lean body mass.[11] Particularly useful would be the employment of available tools for defining hazardous locations of fat deposition. Although simple measures of regional fat distribution, such as waist to hip ratio, have refined our general understanding of obesity and cardiovascular risk, it is not obvious which fat deposition pattern during pregnancy might predict subsequent maternal and child health outcomes. In the Coronary Artery Risk Development in Young Adults study, increasing parity was associated with central adiposity in women,[12] and in nationally representative cross-sectional data, it was shown that breastfeeding duration of 7 months or longer was associated with smaller maternal suprailiac and thigh skinfolds and smaller hip and thigh circumferences.[13] Because long-chain polyunsaturated fatty acids are concentrated in lower body fat, Lassek and Gaulin hypothesized that fat from this region is preferentially mobilized in lactation to support infant brain development. Hence, breastfeeding is a maternal behavior that has potential effects on both maternal pregnancy-related weight[14] and fat distribution, as well as on child health outcomes, thus, underlining the importance of the dyadic relationship that distinguishes maternal obesity from other adult obesity.

Is Obesity a Proxy for Other Factors?

The second conceptual problem is that it is unclear whether obesity per se is the entity that causes adverse outcomes, or whether obesity is only a marker for other factors that are the real agents of disease, such as diet and physical activity. On the one hand, we now know that adipose tissue contains many hormonal factors (eg, leptin, adiponectin) that may play a direct deleterious role in offspring exposed to an obesigenic fetal environment.[15] On the other hand, the causal pathway that leads to energy imbalance stems from a complex mix of ecological factors and individual lifestyle behaviors,

ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
BMI	Body mass index
CP	Cerebral palsy
NDD	Neurodevelopmental delay
RR	Relative risk

making it extremely difficult to tease out direct effects. For example, in a phenomenon now commonly referred to as the hunger-obesity paradox, we find that when hunger and obesity coexist in the same individual, an imbalance in nutrient intake leads to a state of "mal" nutrition characterized by a surfeit of energy, but a deficit in micronutrients.[16] Because maternal nutrient deficiencies, such as iodine, can affect offspring development, maternal obesity might affect child development via nutritional deficiency, not nutritional excess.[17]

How Should We Handle the Time-Varying Nature of Obesity?

A third concept to be borne in mind when thinking of child outcomes in relation to maternal obesity is the time-varying nature of body composition, which requires us to take a life-course approach to maternal obesity. Pregnancy-related weight requires consideration of prepregnancy weight (the most common time point chosen for studying effects on child health), gestational weight gain, and postpartum weight retention. The latter measure impacts upon the prepregnancy weight of subsequent pregnancies (and thus indirectly on the health of offspring) and is also affected by breastfeeding duration. When we posit that maternal obesity is deleterious to offspring, we ought also to ask which of these time windows has the greatest effect on child health.

With increasing evidence of adverse outcomes, both metabolic and neurodevelopmental, accompanying maternal obesity, further studies will be necessary to understand underlying mechanisms. Although significant weight loss for most patients prior to conception is challenging if not impossible, changes in dietary intake and physical activity, achieving appropriate weight gain during pregnancy, and increasing breastfeeding may all be reasonable, achievable goals. But to make clinical and policy recommendations, it will be necessary to determine which of these changes would be most beneficial to mothers and their offspring.

Maternal Obesity and CP

In a California-linked database of 6 million births, Crisham-Janik et al found a relationship between risk of CP and the *International Classification of Diseases* diagnosis of maternal obesity recorded in hospital discharge abstracts either in the year prior to giving birth or at the birth of the index child.[18] A dose-response relationship was seen, with any diagnosis of maternal obesity carrying a relative risk (RR) of 1.30 (95% CI 1.09-1.55) for CP. With any diagnosis of morbid obesity, the RR was 2.70 (CI 1.89-3.86). Neither association was much attenuated by adjustment for maternal race, age, education, prenatal care, or insurance status. The association was largely due to the especially strong association found for mothers whose diagnosis of obesity was based on a hospitalization prior to pregnancy. In such mothers, the RRs linking obesity and morbid obesity, respectively, to CP, were 1.72 (CI 1.25-2.35) and 3.79 (CI 2.35-6.10). For obesity diagnoses obtained at the birth of the child, no significant relationship to CP was found.

Of interest, the prevalence of obesity in the maternal population studied (1%) was well below the estimated rate of obesity in the state during that time frame (10%-14%), probably because the diagnosis was made based on the presence of 3 *International Classification of Diseases* codes: obesity of pregnancy (646.1), unspecified obesity (278.0), and morbid obesity (278.01), rather than on recorded BMI.

In a study of maternal obesity derived from BMI recorded on birth certificates and linked to Medicaid data in South Carolina, Pan et al found, in some 87 000 mother-infant pairs, a steady incremental increase in CP risk by maternal weight—the ORs were 1.15 (CI 0.66-2.01) for overweight, 1.62 (CI 0.90-2.93) for mild obesity, 2.00 (CI 1.00-4.01) for severe obesity, and 2.95 (CI 1.45-5.97) for morbid obesity.[19] Only the last 2 ORs were statistically significant, and for the subset of cases (n = 53) with CP confirmed based on having been recorded more than once in Medicaid records, only the association with morbid obesity was significant (OR = 3.0 [CI;1.09-8.37]).

Ahlin et al found a modest association of maternal BMI, as recorded in obstetric records, with term-born spastic CP in Western Sweden.[20] Mean BMI of mothers of children with spastic CP was 24.0, and in matched controls, 23.0. Each unit increase in maternal BMI raised the risk of CP by 7%. Their report does not make clear when maternal BMI was assessed. Another measure, maternal weight at 34 weeks of gestation, was also associated with CP with each kg of additional weight adding 2% to the risk of CP.

Maternal Obesity and Autism

In 2012 a case-control analysis found an association between maternal obesity, defined as BMI ≥30 based on prepregnancy reported or documented weight, and developmental outcome defined as including both neurodevelopmental delay (NDD) and autism spectrum disorder (ASD).[21] This study found that the risk of developing ASD (OR 1.67; CI 1.10-2.56) and NDD (OR 2.08; CI 1.20-3.61) was increased in offspring of obese mothers compared with controls. The study did not assess pregnancy weight gain. Another recent case-control study, identified ASD cases in a Utah state-wide birth cohort, and compared them with sex- and birth year-matched controls.[22] This study found an association between increased pregnancy weight gain and risk of ASD in the offspring, with or without comorbid NDD. In this study, the mean maternal prepregnancy BMI (based on height and weight at pregnancy onset) in cases and controls was in the normal range, and the difference in pregnancy weight gain between the 2 groups was 3 pounds. Thus, if the maternal metabolic environment is implicated in cognitive and behavioral development, it is unclear whether prepregnancy BMI or pregnancy weight gain, or both, are implicated.

Dodds et al, utilizing a linked database cohort of infants born in Nova Scotia, Canada between 1990 and 2002, found that following adjustment for genetic susceptibility for autism (defined as having a sibling with autism or a mother

with underlying psychiatric or neurologic illness), maternal prepregnancy weight of >90 kg (adjusted RR = 1.58 [CI 1.26-1.98] compared with those who weighed <90 kg) or pregnancy weight gain of ≥18 kg (adjusted RR = 1.19 [CI 1.02-1.39] compared with those who gained less than 18 kg) were independent risk factors for autism, in the final multivariate model.[23]

In the Norwegian Mother and Child Cohort Study, maternal obesity (BMI ≥30) was only weakly associated with ASD risk, but surprisingly, the aOR for paternal obesity and autistic disorder was 1.73 (95% CI 1.07-2.82), and for Asperger disorder it was 2.01 (95% CI 1.13-3.57).[24]

Maternal Obesity and Cognitive Deficits

Neggers et al studied 355 children of low-income African American women, and found that maternal BMI (measured utilizing prepregnancy weight reported by the patient at the first prenatal visit) was inversely associated with age 5 years IQ (Beta = −0.25, P = .005) and non-verbal ability (Beta = −0.29; P = .01) following adjustment for other covariates (including maternal Peabody Picture Vocabulary Test scores that measures receptive language skills).[25] A secondary analysis of a UK population-based cohort of 19 517 children (Millennium Cohort Study) born 2000-2002 with cognitive testing at ages 5 and 7 years of age, found that maternal prepregnancy BMI (measured utilizing prepregnancy weight and height reported by the patient at interview when child was 9 months old) was inversely associated with children's general cognitive scores at ages 5 (P = .0069) and 7 (P < .0001) years.[26] Regression models of individual cognitive test scores showed that at age 5 years maternal prepregnancy BMI was inversely associated with children's spatial visualization, but no relationship existed between maternal BMI and children's expressive language and nonverbal reasoning. At age 7 years, however, a significant inverse relationship was seen between maternal BMI and each of the 3 cognitive assessments: verbal ability, spatial visualization, and number skills. This study adjusted for maternal and paternal education level but not maternal IQ scores.

Heikura et al followed 2 birth cohorts in Northern Finland, one from 1966 (n = 12 058) and the other from 1986 (n = 9432), examining the association between maternal sociodemographic factors and intellectual disability in offspring in each.[27] Prepregnancy maternal obesity (based on prepregnancy weight reported by the mother) was found to be associated with mild intellectual disability (IQ 50-70) in offspring (aOR = 2.8; CI 1.5-5.3) compared with women with normal BMI (20-24.9 kg/m^{2}) but only in the latter cohort. In the earlier cohort, maternal obesity was not associated (aOR 0.5, CI 0.1-3.8) with intellectual disability. Adjustment made for maternal education, and maternal IQ scores were not available. Tanda et al, adjusting for maternal and child factors (including maternal scores on the Armed Forces Qualification Test—a cognitive function test that assesses arithmetic reasoning, word knowledge, paragraph comprehension, and mathematics knowledge), family background, and intra-

uterine factors, found an inverse association between maternal prepregnancy obesity (calculated from reported height and prepregnancy weight), but not overweight, with child cognitive test scores that included reading scores 0.23 SD units lower, and mathematics scores 0.16 SD units lower, than in children of women with BMI's between 18.5-24 kg/m^{2}.[28]

The nationally representative Early Childhood Longitudinal Study is a prospectively collected birth cohort that followed children from birth (in 2001) to kindergarten for the assessment of early development and academic performance. This cohort provided the opportunity to compare cognitive function in offspring of obese mothers vs those of nonobese mothers (study design similar to previously published study); obesity was based on prepregnancy weight.[29] Lower cognitive function was noted in offspring of obese mothers compared with offspring of nonobese mothers in 3 of the 4 time points at which cognitive assessments were made. Differences were found at ages 9 months (0.19 z-units lower, P = .001), 2 years (0.109 z-units lower, P = .002), 3.5 years (0.126 z-units lower, P = .019), and 5 years (0.079 z-units, P = nonsignificant). Adjustment was made for maternal education level but maternal IQ scores were not assessed.[30]

Maternal Obesity and Behavioral and Psychiatric Disorders

Utilizing prospective pregnancy cohorts from Sweden, Denmark, and Finland, teachers and mothers rated 12 556 school-aged children for attention deficit hyperactivity disorder (ADHD) symptoms. Following adjustment for several factors (gestational age, birth weight, weight gain, pregnancy smoking, maternal age, maternal education, child sex, family structure, and cohort country of origin) prepregnancy BMI (determined from maternal weight recorded at first prenatal visit, which was approximately 10 weeks gestational age) was found to be associated with teacher-reported ADHD symptom score in children in dose-response fashion (overweight [BMI 25-29.99 kg/m^{2}] aOR 1.37 [CI 1.07-1.75]; obesity [BMI ≥30 kg/m^{2}] aOR 1.89 [CI 1.13-3.15]). Children of women who were both overweight and gained excess weight during pregnancy had a 2-fold (OR 2.10; CI 1.19-3.72) increased risk of ADHD symptoms compared with offspring of normal-weight women.[31] This study was re-analyzed using more extensive adjustment, including additional potential confounding variables such as maternal distress, parental ADHD symptoms, and child overweight. The findings were unchanged.[32]

A review of 4 population-based studies of prepregnancy maternal BMI and schizophrenia, which included a total of 305 cases of schizophrenia and 24 442 controls, provided findings on obesity in 3 studies, and BMI was examined only as a continuous variable in one study.[33] Of these 4 studies, the Finnish 1966 birth cohort study noted a nonsignificant aOR of 2.1 (CI 0.9-4.6) for risk of schizophrenia in children of mothers with BMI >29 compared with children of mothers with BMI 19.1-29, after adjustment for sex, social class, and maternal age at conception. BMI was determined from records

from home visits or prenatal clinics. A cohort from the US found a significant OR of 2.9 (CI 1.3-6.6) for schizophrenia in children of mothers with BMI >30 compared with BMI 20.0-26.9; BMI collected from medical/antenatal clinic records; this significance remained after adjustment for maternal age, ethnicity, parity, smoking, and education. A Japanese study found a 24% increase in risk of schizophrenia in adult offspring per unit increase in maternal BMI (collected from mother and child handbook completed during pregnancy) measured in early pregnancy; case and control mothers did not differ significantly for those variables studied (age, physical illness, or gestational age at the time of first and last antenatal visit). The remaining study, also from Finland, found, however, an OR of 3.75 (CI 1.42-9.89) for schizophrenia in offspring whose mothers had a lower BMI (<24) compared with those with BMI >30 (collected from birth records). For the Finnish study, mothers of adult offspring with schizophrenia were more likely to smoke, report depressed mood, and have diabetes during their pregnancy. There was no mention within the review of the presence of maternal schizophrenia in cases or controls for these studies.

Potential Mechanisms by Which Maternal Obesity Might Exert Effects on Neurodevelopment

Human neurodevelopment occurs primarily in fetal and early postnatal life. The fetal environment has, therefore, long been considered fertile ground for searching for risk factors for neurodevelopmental disorders. With a growing but not entirely consistent literature documenting a relationship between maternal obesity and NDD and behavioral abnormalities in offspring, the paramount question is whether obesity is simply a marker of other causal factors or a true cause of these findings. Any analysis, therefore, of the possible causal contribution of maternal obesity to childhood outcomes, must attempt to take account of the broader social and biological context in which obesity is embedded, as well as the dietary and physical activity contributions to caloric balance that create obesity in the first place. Most studies, therefore, make considerable efforts to adjust for other potentially confounding factors. Three of the studies we reviewed adjust for both prenatal and postnatal factors.[23,27,32] Their findings of an obesity-neurodevelopment association persisting after such adjustment increases the likelihood that maternal obesity during gestation may play a direct role in offspring neurodevelopment. Nevertheless, the complexity of the interaction of obesity with many other factors of interest may limit our ability to tease out its independent risk. We know, for example, that the association of African American ethnicity with a number of adverse outcomes has often been found even after adjustment for a myriad of social and economic factors, in part because it is so difficult to measure the chronic social and individual stresses that accompany African American ethnicity. A similar dilemma confronts the analysis of maternal obesity.

The mechanism by which maternal obesity may contribute to abnormal neurodevelopmental or behavioral outcomes remains largely unknown. Several factors, however, have been implicated. Dietary intake may play a direct role, for example by excess intake of free fatty acids or glucose, or via micronutrient deficiencies of Vitamin D, B12, folate, iron, or other metabolites. Glucose, for instance, is a known teratogen, well known to be related to birth defects with uncontrolled diabetes in early pregnancy.

Rodent studies have demonstrated that some diets may affect maternal behavior. In particular, high-energy diet disrupts maternal hippocampal function, which in turn influences learning and memory in the offspring. The obese state is noted to be associated with anxiety and depression; healthy diet may improve behavior in the mother (such as reducing postpartum depression in human studies).[34] The possible effect of depression associated with obesity is highlighted by rodent studies showing that mothers who perform less licking/grooming and arched-back nursing behavior and lack attentive behavior have offspring with increased anxiety-like behavior, and experimental manipulation of epigenetic modification in adult offspring (via delivery of histone deacetylase or methyl donors) modulated anxiety-like behavior, suggesting a potential epigenetic mechanism.[35] This could provide a mechanism for transgenerational propagation of obesity, as the exposed offspring may participate in another cycle of reward-based eating, because studies show that a palatable, high-fat diet reduces anxiety-like behaviors by increasing glucocorticoid receptor messenger RNA expression in the hippocampus.[36]

Another area to consider in relation both to maternal obesity and to high-fat diets is inflammation. The impact of the inflammatory state on offspring neurodevelopment has been extensively described, particularly in relation to intrauterine infection (chorioamnionitis) and outcomes such as CP.[37] Obesity is itself a systemic inflammatory condition, with chronic activation of the innate immune system signaled by the presence of high-levels of inflammatory cytokines. Rat dams exposed to high-fat diets demonstrated hippocampal changes in the offspring, as well as increases in anxiety, spatial learning, and chronic increases in proinflammatory cytokine expression through to adulthood.[38] Studies utilizing the nonhuman primate model have also demonstrated that maternal high-fat diet consumption during pregnancy leads to lipotoxicity in the fetus, with high levels of circulating inflammatory cytokines and evidence of fatty liver disease.[39] Furthermore, neurotransmitter systems that are important for behavioral regulation, such as the serotoninergic and dopaminergic systems, have been shown to be sensitive to circulating inflammatory cytokine levels.[40]

Recommendations for Further Research

Whatever the end-point of interest in studies of neurodevelopment in relation to maternal obesity, some key considerations may help in the design of studies to advance our understanding.

Data must be collected on the context in which obesity occurs—maternal education and intelligence, socioeconomic status, use of tobacco and other products, early childhood experiences, emotional states, especially depression, and, of course, diet and physical activity, are just some of the factors that should be assessed before concluding that obesity itself is exerting a direct and independent effect on offspring neurodevelopment. Factors associated with both obesity and neurodevelopment must be carefully scrutinized for the possibility that they may explain the observed association.

Maternal obesity contains at least 3 components that should be measured directly whenever possible—prepregnancy obesity, pregnancy weight gain, and postpartum weight. Although the role of postpartum weight loss may at first glance seem extraneous, the extent to which mothers return to baseline weight after pregnancy may reflect stress, depression, breast-feeding, or other factors, and also influences prepartum obesity in subsequent pregnancies.

The incorporation of measures of body fat into the definition of obesity would greatly enhance our understanding. Addressing this problem in pregnancy is considerably more complex than at other times in the life cycle. Creative approaches to measurement of fat mass and lean body mass over the reproductive cycle are to be encouraged.

Molecular biomarkers—genetic polymorphisms, patterns of gene expression, epigenetic modifications, hormones, and other biomarkers—should be explored more thoroughly in attempts to shed light on mechanisms underlying observed epidemiologic associations.

The findings of intervention studies targeting 1 or more of the 3 components of maternal obesity and measuring neurodevelopmental outcomes might help unravel some of the mechanisms governing this association.

Discussion

Evidence is growing that a relationship exists between the maternal milieu represented by obesity and adverse neurodevelopmental, behavioral, and psychiatric outcomes in offspring. Given the high prevalence of obesity in today's world, continued research is needed both on the nature of this relationship as well as on the potential etiologies and mechanisms by which it is operating. ∎

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