HHS Public Access

Author manuscript

J Perinatol. Author manuscript; available in PMC 2015 March 01.

Published in final edited form as:

J Perinatol. 2014 September ; 34(9): 688–692. doi:10.1038/jp.2014.80.

Maternal Obesity and Increased Risk for Autism and Developmental Delay among Very Preterm Infants

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Abstract

Objective—Thirty-five percent of women of child-bearing age are obese, and there is evidence that maternal obesity may increase the risk for adverse neurodevelopmental outcome. However, research regarding obesity and neurodevelopment among children born preterm is limited. This study aimed to determine associations between maternal obesity and neurodevelopment in very preterm children at age 2 years.

Study Design—Maternal/infant dyads (n=62) born ≤30 weeks gestation were enrolled in a prospective cohort study at a level-III neonatal intensive care unit. Mothers were classified as obese or non-obese based on pre-pregnancy body mass index. Infants underwent magnetic resonance imaging at term equivalent and developmental testing at age 2. Maternal obesity was investigated for associations with neurodevelopment.

Results—Maternal obesity was associated with positive screen for autism (OR=9.88, p=0.002) and lower composite language scores (β=-9.36, [CI=-15.11, -3.61], p=0.002).

Conclusion—Maternal obesity was associated with adverse neurodevelopmental outcome at age 2 in this cohort of very preterm children. This study requires replication, but may support targeted surveillance of infants born to women with maternal obesity.

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There are no conflicts of interest.

Keywords

neonatal intensive care; premature infant; body mass index; neurodevelopment; developmental delay

INTRODUCTION

In the United States, the rate of obesity is steadily rising.(1, 2) Among women of child-bearing age, approximately 64% are overweight and 35% are obese.(3) Maternal obesity is a predictor of adverse health conditions in pregnancy; such as preeclampsia, gestational diabetes, inflammation and increased risk for maternal death.(4) Subsequently, the hospital costs associated with childbirth for women with maternal obesity is an average of $4000 more than among women without obesity.(5) Maternal obesity not only affects maternal health and healthcare expenditure, but it is an important predictor for infant and childhood outcomes. There is evidence that maternal obesity may increase the risk for poor neurodevelopmental outcomes in term born infants. The association between maternal obesity and impaired cognitive development in early childhood has been well defined. (6), (7, 8) Research findings have supported that maternal metabolic conditions, including maternal obesity, are associated with increased risk for autism, developmental delay and impaired language skills.(9) In addition, maternal obesity in animal models has been associated with abnormal brain development, including impaired hippocampal growth, impaired hippocampus progenitor cell division and neuronal production(10) and inflammation.(11) It has been hypothesized that inflammation of the fetal brain could be related to inflammatory processes associated with maternal obesity,(11) which may be a possible mechanism for adverse neurodevelopmental outcomes observed in infants of mothers with a high body mass index (BMI).

While there is burgeoning research investigating the effects of maternal obesity in full term infants, evidence for the relationship between maternal obesity and outcome in preterm children is limited. The results of a single study support that maternal obesity may predict adverse cognitive outcomes in very preterm (VPT) infants,(12) however, the percentage of women in this study with maternal obesity was slightly below the national average. Given that preterm infants are at a high risk for early brain injury and adverse neurodevelopmental outcomes, including autism,(13) it is important to investigate the associations between maternal obesity and adverse outcomes in a preterm population who may be at increased risk. Understanding maternal factors that can result in high risk of neurodevelopmental impairment can improve surveillance measures to enable early intervention service activation, and provide opportunities for maternal education and interventions that can promote health and well-being to both mothers and children.

The aim of the study was to investigate the associations between maternal obesity and neurodevelopmental outcomes in preterm infants. We hypothesized that VPT infants born to women with maternal obesity would have a higher risk of screening positive for autism and have poorer neurodevelopment at age 2 years.

METHODS

This was a prospective cohort study contained in an overarching study that investigated brain development and outcomes in preterm infants enrolled from 2007 to 2010. Study participants (n=62 mother/infant dyads) were a subset of the overarching study who had a calculable maternal BMI and included infants who returned for developmental testing at age 2 years. Participants were born ≤30 weeks estimated gestational age (EGA), were free of congenital anomalies, and were enrolled within the first 72 hours after birth. The study took place in a level III, 75-bed neonatal intensive care unit (NICU) in the Midwestern United States, which serves a large population of urban patients with diverse socioeconomic status.

This study was approved by the Human Research Protection Office at Washington University. Infants were enrolled following informed parental consent. Perinatal infant factors and maternal factors were collected from the medical chart. Magnetic resonance imaging (MRI) was undertaken at term equivalent age. At 2 years of age, the infants returned for developmental follow-up testing. Data were used to investigate the associations between maternal obesity and outcome. Additional analyses investigated associations between maternal obesity and perinatal factors, in addition to maternal obesity and brain structure at term.

Independent Variables – Maternal Body Mass Index and Weight Gain

Body mass index and weight gain—Maternal height, pre-pregnancy weight and pregnancy weight gain were collected from the medical chart. Pre-pregnancy BMI was calculated from height and weight during the first trimester, classified into obese (BMI≥30) and non-obese (BMI<30) and analyzed as a dichotomous variable. Weight gain was adjusted for by length of gestation. It was calculated by dividing the pregnancy weight gain by total weeks of gestation for a measure of pounds per week.

Outcome Measures

Perinatal infant and maternal factors—Baseline infant medical factors collected included gestational age at birth, gender, race, birthweight, head circumference (OFC), weight-for-height/length standard deviation score (SDS), days of ventilation (categorized according to quartiles), length of hospitalization, Critical Risk Index for Babies (CRIB) score (14) and absence/presence of patent ductus arteriosus, retinopathy of prematurity, necrotizing enterocolitis and sepsis. The aforementioned factors were collected due to known associations with brain development and outcomes.(15-25) Factors collected from the maternal medical record included absence or presence of gestational diabetes, hypertension and preeclampsia. In addition, the following measures were collected to create a composite social risk score: family structure, education of primary caregiver, occupation of primary income, employment status of primary income earner, insurance status, and maternal age at birth.

Brain injury—At term equivalent age, participants were escorted to an MRI suite, where MRI was conducted without sedation. MRI findings were combined with routine cranial

ultrasound (CUS). A single neuroradiologist, blinded to infant or maternal health factors, interpreted the MRI images.

Qualitative Assessment of Brain Structure—A standardized scoring evaluation of brain growth and development was applied.(26) In addition to specific types of injury, a dichotomous variable was used to control for brain injury in the statistical model. For this control variable, the presence of brain injury was defined as having either grade III-IV intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL) or cerebellar hemorrhage.

Brain Metrics—Regional brain measures, including bifrontal, biparietal, and transcerebellar diameters, ventricular size, and interhemispheric distance were obtained.(27)

Diffusion—Regions of interest were manually placed using fractional anisotropy (FA), mean diffusivity (MD) and red-green-blue (RGB) maps to identify anatomic structures on three contiguous slices for each infant scan in order to minimize through-slice partial volume averaging, which may contribute to inaccurate diffusion measurements. Anatomic structures sampled included the anterior limb of the internal capsule, posterior limb of the internal capsule, optic radiations, frontal lobe, corpus callosum, cingulum bundle, centrum semiovale, superior and inferior temporal lobe, orbitofrontal cortex. These were sampled for MD, FA, axial diffusivity and radial diffusivity using ANALYZE 10.0 software.

Volumetry—Volumetry was conducted with Advanced Normalization Tools software (ANTS), a multiplatform automated tissue segmentation software package, using methodologies previously described.(28, 29) Images were registered to a neonatal atlas, and tissue types were delineated using tissue probability maps.(30) The ANTs segmented MRI volumes were then manually corrected using ITK-Snap software. The analyst was blinded to patient group.

Surface-Based Analysis—A subset of the cohort was selected for having no significant brain injury and having the best quality scans to conduct surface based analysis. This subset consisted of 13 infants of obese mothers and 23 infants of non-obese mothers. While infants were not matched, analyses confirmed that there were no significant differences in gestational age, birthweight, gender or Critical Risk Index for Babies score(14) among infants of obese mothers compared to infants of mothers without obesity. A semi-automated algorithm, LIGASE,(31) was applied and segmentations were manually edited using CARET software (http://brainvis.wustl.edu) to generate three-dimensional cortical mid-thickness surface reconstructions. Surfaces were then registered to the PALS-term12 version 2 atlas, and sulcal depth analyses between the groups were performed using established methods.(32)

Primary outcome measures

Modified Checklist for Autism in Toddlers—The Modified Checklist for Autism in Toddlers (M-CHAT)(33) is a parent-report screening tool developed to identify children 12 to 36 months of age who are at risk for autism spectrum disorders. The sensitivity and

specificity, for the M-CHAT identifying individuals who screen positive and are later diagnosed with autism, are 0.70 (95% CI = 0.54–0.83) and 0.38 (95% CI = 0.14–0.68) respectively.(34) The M-CHAT was completed by the primary caregiver at age 2 years.(35) Pass/fail scores on the M-CHAT were analyzed.

Bayley Scales of Infant and Toddler Development, 3rd Edition—The Bayley Scales of Infant and Toddler Development is an assessment of language, motor and cognitive development,(36) and was administered at age 2 years by a trained rater. The sensitivity and specificity for the Bayley-III are 58% and 100%, respectively.(37) Composite scores for language, motor and cognitive, along with their subscales of expressive and receptive language and gross and fine motor were analyzed.

Statistical Management and Data Analysis

Data was analyzed using SPSS 20 (IBM Corporation, 1989, 2011). Multivariate linear mixed models and logistic regression were used to determine associations between maternal obesity and 1) neonatal brain structure measures, and 2) short term neurodevelopmental outcome, while controlling for potential confounding factors (2 sided analysis, α=0.01). Statistical models accounted for multiple gestation with use of a Family ID variable that accounted for the clustering between twins/triplets in the analysis. Gender and gestational age at birth were controlled for in all perinatal analyses. Gender and post-menstrual age at scan were entered as covariates in all models assessing neonatal brain measures. Gestational age at birth and markers of sociodemographics were controlled for in the cognitive, motor and language analyses at age 2 years by using a composite Social Risk Score in the model. (38) This score was modified to include insurance status rather than language spoken in the home.

Additional analyses—In obese mothers, independent samples t-tests were used for exploratory analyses to understand perinatal and maternal factor differences in children who failed versus passed the M-CHAT. Brain measures at term equivalent were analyzed as secondary outcome measures to assess whether alterations in brain structure at term equivalent were associated with maternal obesity and potential mediators of adverse neurodevelopmental outcomes at age 2 years. In addition, group differences between obese and non-obese mothers in regards to hypertension and preeclampsia were analyzed using chi-square analysis.

RESULTS

There were 62 infants and 49 mothers (due to multiple gestation pregnancies) included in the final analysis. See Tables 1 and 2 for infant and maternal cohort characteristics.

Neurodevelopmental outcome at age 2 years

The results of the analyses between maternal BMI and neurodevelopmental outcome at age 2 are presented in Table 3. Maternal obesity was associated with lower Bayley-III composite language (β=-9.36, [CI= -15.11, -3.612, p=0.002) with notable effect on expressive language (β=-2.06, [CI= -3.13, -.98], p=<0.001). The mean composite language score for infants born

to non-obese mothers and obese mothers were 92.02 (SD=9.22) and 82.08 (SD=10.79), respectively. There was a strong trend for associations between reduced motor (β=-7.88, [CI=-14.55, -1.21], p=0.02) scores most notably in gross motor (β=1.76, [CI=-3.10, -.43], p=0.01) scores. The mean composite motor score for infants born to non-obese mothers and obese mothers were 86.10 (SD=10.03) and 76.48 (SD=13.18), respectively. Maternal obesity was also associated with failures on the M-CHAT (OR=9.88, [CI=0.88, 3.70], p=0.002). 11.9% of non obese mothers had a child fail the m-chat compared to 58.8% of obese mothers. Cognitive and fine motor scores were not associated with maternal obesity.

Maternal obesity and M-CHAT results

In addition, analyses evaluating differences between obese mothers whose children had failed or passed the M-CHAT indicated a difference in gestational age at birth between the two groups, t(2.36)=22, p= 0.03. These results suggest that obese mothers of children who failed the M-CHAT had given birth earlier in their pregnancy (mean=26.08 weeks; SD=1.50) than mothers of children who passed the M-CHAT (mean=27.67; SD=1.78). As noted in the above multivariate analyses (see Table 3), maternal obesity remained significant when adjusted for the gestational age at birth.

Neonatal brain structure

Brain measures of injury, metrics, volumetry and surfaces at term equivalent age were not associated with maternal obesity. Maternal obesity was associated with fractional anisotropy diffusion in the region of the right inferior temporal lobe (p=0.005); however it was no longer statistically significant after Bonferroni correction (α=0.004) was applied to the analysis to correct for multiple comparisons. Maternal obesity was not associated with any other diffusion measures.

Perinatal factors

Infant OFC and SDS were not associated with maternal obesity. Maternal weight gain (adjusted for months of gestation, pre-pregnancy BMI, and admission weight) also was not associated with neurodevelopmental outcomes.

A secondary analysis was performed after finding the relationship with maternal obesity and neurodevelopmental outcome, to determine if this was mediated by hypertension and preeclampsia, which occur at a higher rate in women with maternal obesity.(39) There was no association found between gestational diabetes and infant outcome at age 2. There was a significant difference in rates of hypertension and preeclampsia in obese mothers compared to the non-obese mothers (Table 2); therefore, these factors were individually adjusted for in the models. Maternal obesity remained a predictor of language outcomes (see Table 3), while neither hypertension nor preeclampsia were associated with infant outcome at age 2 years in this study (p<.01)).

DISCUSSION

The key finding is that maternal obesity was associated with an increased risk of screening positive for autism and was associated with developmental delay, specifically alterations in

language skills, at 2 years of age. Neither maternal pregnancy weight gain nor maternal obesity was associated with perinatal factors or measures of neonatal brain structure. In addition, the maternal co-morbid conditions of gestational diabetes, hypertension and preeclampsia were not predictive of neurodevelopment in this cohort.

The results of our study support previous findings in the literature that report an association between maternal obesity and developmental delay in early childhood.(8, 9) Decreased overall language scores were associated with a maternal BMI ≥ 30. Maternal obesity was associated with a trend toward impaired motor skills, particularly gross motor development, which is a novel finding in VPT infants. Impaired motor skills have been linked to maternal obesity in term born children.(9) In addition, our findings suggest that maternal obesity is associated with the risk for positive autism screen at age 2 years. Previously, it has been reported that maternal metabolic conditions including obesity are associated with developmental delays, including decreased language skills and an increased likelihood of autism spectrum disorders.(9, 40)

Interestingly, an analysis of women with maternal obesity in relation to child M-CHAT results revealed that there was a difference in gestational age between children who failed or passed the screen. Children who passed had a higher mean gestational age than those who failed the autism screen, which could indicate additional support for the relationship between a lower gestational age and risk of autism.(41) Nevertheless, maternal BMI remained an independent risk factor as it remained significant in the analyses after adjusting for gestational age. This, compounded with the effects of maternal obesity, is an area of research requiring further exploration.

In contrast to other developmental outcomes, cognitive scores were not associated with maternal obesity in our cohort of VPT infants. This finding is contrary to other published literature on maternal obesity and outcomes.(7, 8, 12) Possible differences may include the established high risk of later cognitive problems in preterm infants(42) or perhaps the delayed emergence of stronger associations between maternal obesity and the cognitive skills of older children.(7, 43) In addition, the Bayley-III has been identified as potentially underestimating cognitive problems in preterm children when compared to the previous 2nd edition,(44, 45) which was used to measure cognitive outcomes in the singular study reporting the relationship between maternal obesity and cognitive impairment in preterm infants.(12) Following this cohort and assessing cognition later in childhood, when cognition may be a more stable marker for longer term outcome, is planned and will be important.

Although pre-pregnancy BMI was associated with adverse developmental outcomes, maternal weight gain during pregnancy was not. This finding differs from recent literature in term born infants, which supports an association between increased weight gain and greater risk for autism spectrum disorders.(9) The gestation of pregnancy is clearly shorter in preterm pregnancies and weight gain may be affected by length of pregnancy. The Institute of Medicine currently recommends a weight gain of one pound per week in the third trimester, and mothers that were more than a few weeks into the third trimester (30 weeks PMA) were excluded from this study. The mothers in our study would have ideally gained at least 7- 13 additional pounds if their pregnancy had been full term. This may also explain

why measures of infant head circumference and birthweight were not associated with maternal obesity or weight gain in our cohort, which is in contrast to a recent study linking a higher maternal weight gain with higher birthweights and large for gestational age infants in normal gestation pregnancies.(46)

Neuroimaging measures of neonatal brain structure at term equivalent were not associated with maternal obesity. Of note, on measures of diffusion, specifically the area of the right inferior temporal lobe was associated with maternal obesity, which included white matter adjacent to the hippocampus; however, after adjustment for multiple comparisons, the relationship did not remain significant. While many brain measures were undertaken, we did not gather measures of the hippocampus, the region most implicated in animal models of maternal obesity,(10, 11) due to challenges in segmentation in the newborn brain. Further research investigating brain measures in the offspring of women with maternal obesity is necessary to understand the associations between BMI and brain development.

Limitations

Limitations in this study included a small sample size and the possible ambiguity of M-CHAT results. For preterm children who are screened with the M-CHAT, some have suggested that a positive result may instead indicate developmental delay and behavioral differences not attributed to autism.(47) Children with autism born full term, however, are also at increased risk of motor and language deficits.(48, 49) Thus, it remains unclear if the M-CHAT is detecting other developmental delays. This will be followed up in a subsequent study investigating outcomes at age 5 years, when an autism diagnosis will be assessed through structured assessments. Finally, this study is limited by failure to track weight gain at various time points throughout the pregnancy, which could have provided additional insights.

CONCLUSION

Previous studies have suggested that maternal obesity may increase the risk of preterm birth; therefore it is a risk factor that is worth further investigation to determine how maternal obesity relates to the increased rate of autism spectrum disorders and developmental delay among preterm children. This study demonstrates that maternal obesity is associated with a positive screen for autism and developmental delay in VPT children at age 2 years. While requiring replication, our findings support targeted surveillance of VPT infants born to women with maternal obesity to ensure that services are initiated early in their developmental trajectory, as well as preconception and prenatal counseling for women of child-bearing age. Identification of the risks of maternal obesity on the development of preterm infants may improve neurodevelopmental outcomes by pre-emptively addressing BMI before conception.

Acknowledgments

We wish to acknowledge Karen Lukas RN (Washington University School of Medicine), Anthony Barton (Washington University School of Medicine), Jessica Conners (Washington University School of Medicine), Dimitrios Alexopolous MS (Washington University School of Medicine), Joe Ackerman, Jr. (Washington University School of Medicine), Claudine Vavasseur MD (National Maternity Hospital, Dublin Ireland) and Han

Tjoeng MD (University of Hawaii) who obtained informed consents and conducted patient oriented responsibilities to support the success of this project. We also wish to thank all the families whose infants participated in this study.

Funding: This project was supported by the National Institute of Health (ROI HD 057098), the Doris Duke Foundation, the Washington University Intellectual and Developmental Disabilities Research Center (NIH/NICHD P30 HD062171), and the UL1 TR000448, sub award KL2 TR000450 from the National Center for Advancing Translational Sciences

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Abbreviations

VPT	very preterm
M-CHAT	Modified Checklist for Autism in Toddlers
Bayley-III	Bayley Scales of Infant and Toddler Development 3rd edition
BMI	body mass index
NICU	neonatal intensive care unit
MRI	magnetic resonance imaging

Table 1

Infant cohort characteristics.

Infant	Whole Cohort (n=62)	Born to Obese Mothers (n=24)	Born to Non-Obese Mothers (n=38)	P value *
Gestational age at birth, weeks, M (SD)	26.74 (1.64)	26.88 (1.8)	26.66 (1.55)	0.62
Sex				
Male, N %	38 (61.3)	8 (33.3)	16 (42.1)	0.50
Race				
White, non-Hispanic, N %	32 (51.6)	11 (45.8)	21 (55.3)	0.73
African American, N %	26 (41.9)	12 (50)	14 (36.8)	
Other, N %	4 (6.5)	1 (4.2)	3 (7.9)	
Length of stay (days), M (SD)	85.19 (24.19)	80.09 (27.03)	88.97 (21.53)	0.19
Brain injury, N %	12 (20.7)	4 (18.2)	8 (22.2)	0.72
Sepsis, N %	17 (31.5)	5 (21.7)	12 (38.7)	0.13
Patent ductus arteriosus, N %	28 (51.9)	13 (56.5)	15 (48.4)	0.56
Necrotizing enterocolitis, N %	2 (3.7)	1 (4.2)	1 (3.2)	0.83

* P value investigating differences in perinatal factors among obese and non-obese mothers using independent samples t-tests and chi-square analyses.

Table 2

Maternal cohort characteristics.

Mother	Whole Cohort (n=49)	Obese Mothers (n=17)	Non-Obese Mothers (n=32)	P value *
Maternal BMI, M (SD)	27.84 (8.58)	37.38 (6.67)	22.77 (3.82)	<0.001
Obese (≥30) n (%)	17 (34.7)	17 (100)	0 (0)	
Maternal age, M (SD)	27.72 (5.64)	28.56 (5.51)	27.22 (5.75)	0.51
Maternal pregnancy weight gain (lbs), M (SD)	22.98 (14.01)	30.19 (18.88)	19.38 (9.2)	0.002
Insurance type, N %				
Public Aid	31(63.3)	13 (76.5)	18 (54.5)	0.052
Maternal education, N %				
> 12 years	23 (60.5)	6 (50)	17 (65.4)	0.26
Gestational diabetes, N %	3 (6.3)	3 (17.6)	1 (3.0)	0.003
Hypertension, N %	17 (35.4)	9 (52.9)	8 (25.0)	0.008
Preeclampsia, N %	15 (31.3)	9 (52.9)	6 (18.8)	0.002

* P value investigating differences in maternal factors among obese and non-obese mothers using independent samples t tests and chi-square analyses.

Table 3

Associations between maternal obesity, risk for autism and developmental delay.

BMI (dichotomous)	Beta or Odds Ratio	Confidence Interval (95%)	P value*
M-CHAT	9.875 (OR)	0.88, 3.70	**0.002**
Bayley-III Cognitive Composite	-3.85	-9.38, 1.68	0.17
Bayley-III Language Composite	-9.36	-15.11, -3.61	**0.002**
Bayley-III Motor Composite	-7.88	-14.55, -1.21	**0.02***

* P value investigating differences in 2 year outcome among obese and non-obese mothers, using linear mixed models and logistic regression.