Maternal Plasma Folate Levels in Pregnancy and Early Childhood Cognitive and Language Development

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The Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) Study
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Background

- Fetal central nervous system (CNS) development is reliant on the adequacy of the maternal micronutrient folate levels. Folate is a water-soluble vitamin which is involved with cell proliferation, CNS repair, and gene expression.
- Folic acid supplementation during pregnancy has been shown to prevent certain neurologic defects. Public Health agencies recommend supplementation with folic acid before & during pregnancy and many countries fortify the food supply.
- Researchers have recently published that maternal folate acid supplementation may be associated with lower risk of severe language delay & autism spectrum disorder.
- Maternal folic acid supplementation in early pregnancy has been found to be associated with reduced risk of severe language delay at three years (Roth, et al; JAMA, 2011). However, the sample size (Norwegian Mother and Child Cohort Study) and reduced risk of autism spectrum disorders (Suren, et al, 2013) including 370 children from the same Norwegian sample. (JAMA, 2013)
- Schmidt et al. published that folate intake (as measured by diet records and supplement use) was lower in the first month of pregnancy for mothers of children with autism compared to children without autism (American Journal of Clinical Nutrition, 2011). This association was stronger for mothers and children with certain variant genotypes for inefficient folate metabolism.

Purpose

- To determine if maternal plasma folate (MPF) levels during pregnancy are related to cognitive and language outcomes at 2 years old.

Methods

- The Conditions Affecting Neurocognitive Development and Learning in Early childhood (CANDLE) Study is a prospective, longitudinal, community-based study of 1503 mother-infant dyads from mid-gestation into early childhood. The sample is representative of the population of Memphis, Shelby County, TN. Mothers were recruited during the 16-26th weeks of a single, live-born, singleton pregnancy.
- Maternal plasma folate measures were obtained. The retention rate was 77% for the 2 year old child visit, and children are followed to older ages (around 4 years old in 2014).
- Maternal cognitive and language development was measured by the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley) at 2 years in 1090 children.
- Child sex, race, age at delivery, maternal education, insurance, depression, genotypes for inefficient folate metabolism, and supplement use was lower in the first month of pregnancy for mothers of children with autism compared to children without autism (American Journal of Clinical Nutrition, 2011). This association was stronger for mothers and children with certain variant genotypes for inefficient folate metabolism.

Demographics & Variables

<table>
<thead>
<tr>
<th>Sample size</th>
<th>1090</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at delivery</td>
<td>Mean 31.8, SD 5.6</td>
</tr>
<tr>
<td>Maternal IQ</td>
<td>Mean 105</td>
</tr>
<tr>
<td>Maternal educational attainment</td>
<td>Mean 15.0 years</td>
</tr>
<tr>
<td>Maternal marital status</td>
<td>Married/Living with partner 99.7%, Single 0.3%</td>
</tr>
<tr>
<td>Maternal employment status</td>
<td>Full-time 87.2%, Part-time 12.8%</td>
</tr>
<tr>
<td>Maternal insurance</td>
<td>Medicaid 55%, Other/None 45%</td>
</tr>
<tr>
<td>Maternal smoking status</td>
<td>Non-smoker 98.5%, Smoker 1.5%</td>
</tr>
<tr>
<td>Maternal depressive symptoms</td>
<td>Mean 4.8, SD 3.5</td>
</tr>
<tr>
<td>Maternal dietary intake</td>
<td>Folate 400 mcg/d</td>
</tr>
</tbody>
</table>

Results

Correlations were computed in bivariate analyses to examine the relationship between each outcome (Cognitive and Language Composite Scores) and the independent variables.

General linear models were used to determine significant predictors of Cognitive and Language Composite Scores.

Based on the bivariate analyses, maternal depressive symptoms (BSI at the prenatal or 2 years clinic visit) were not included in the final regression model; other predictors were statistically significant and therefore were included in the final model.

Bivariate Analysis Results

Bayley Cognitive and Language Composite scores (and Receptive and Expressive Scaled scores) were correlated with Maternal plasma folate during the 2nd and 3rd trimesters. This correlation was significant (p<0.001) but not strong (r=0.25).

Linear Models Results

Maternal plasma folate in the 2nd trimester (though not the 3rd) was a statistically significant predictor for Bayley Cognitive Composite scores (p=0.0120). Maternal plasma folate measures were not significant predictors of Language Composite scores (or Receptive or Expressive Scaled scores).

In addition to the association with folate, other predictors of Cognitive composite score included child’s gender; mother’s race, IQ, and parent-child interaction (p=0.36); predictors of Language score included mother’s insurance and report of any breastfeeding in the first year of life (p=0.27).

Predicators of Cognition at 2 years old p-value

- Maternal Race <.0001
- Maternal IQ <.0001
- Parent Child Interaction <.0001
- Child’s Sex .0006
- Maternal plasma folate 2nd trimester .0120

Predicators of Language at 2 years old p-value

- Maternal Race <.0001
- Maternal IQ <.0194
- Parent Child Interaction <.0001
- Child’s sex <.0001
- Insurance type .008
- Ever breastfed during 1st year .0041

References


Conclusion & Discussion

- Maternal plasma folate levels were positively associated with cognitive, but not language outcomes, in 2-year-old children.
- Maternal plasma folate levels were not significant predictors of any of the language measures at two years of age in this study after controlling for known confounding variables.
- While this study benefits from a relatively large sample size and multiple measures for both mother and child at various time points, certainly it remains difficult to ascertain precise effects from an array of potentially important variables. Many of these important variables were included in the analysis for this study and several were found to be also significant predictors of cognitive and language outcomes (as shown in tables).
- Since mild language delays and/or those seen in Autism Spectrum Disorders may not be evident until after 2 years of age, research is ongoing to evaluate developmental outcomes at older ages as well. It is critical to continue to invest in gestational folate supplementation to help improve outcomes for children who may be at risk to develop additional features of Autism Spectrum Disorder.
- Further research to explore potential implications on preconceptual pregnancy planning and prenatal care is warranted.

Acknowledgements

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The CANDLE Study www.candlestudy.org
The Urban Child Institute www.urbanchildinstitute.org
The University of Tennessee Health Science Center, Memphis www.uthsc.edu