RESEARCH LETTER

Hemoglobin A1c Levels During Pregnancy and Risk of Autism Spectrum Disorders in Offspring

Maternal preexisting type 1, type 2, or gestational diabetes diagnosed relatively early in pregnancy are associated with increased risk for autism spectrum disorders (ASDs) in offspring. This study extends previous observations by examining the association between maternal hemoglobin A1c (HbA1c) levels during pregnancy and risk of ASD in offspring.

Methods | This retrospective cohort study included singleton children born at 28 to 44 weeks’ gestation in Kaiser Permanente Southern California (KPSC) hospitals between January 1, 2012, and December 31, 2013. KPSC implemented HbA1c screening in the early prenatal period for all pregnancies starting in 2012. Children who enrolled as KPSC health plan members at age 1 year were tracked through electronic medical records until the first of the following: (1) clinical diagnosis of ASD with at least 1 diagnostic code, (2) last date of continuous KPSC membership, (3) death, or (4) study end date of December 31, 2017. The KPSC institutional review board approved this study and provided waiver of participant consent.

The last HbA1c level in the first 2 trimesters of pregnancy was obtained from the electronic laboratory database. HbA1c was analyzed as a continuous variable and a categorical variable classified as less than 5.7%, 5.7% to 5.9%, 6.0% to 6.5%, and greater than 6.5%. Methods to identify ASD were previously described. Cox regression was used to estimate hazard ratios of ASD associated with HbA1c exposure. Kaplan-Meier plots were used to display the crude cumulative incidences of ASD by the HbA1c categories. Potential confounders listed in the Table footnote “a” were evaluated. Interaction with gestational age at HbA1c testing was also assessed. SAS Enterprise Guide version 7.1 (SAS Institute Inc) was used for data analysis. A 2-sided P < .05 was considered significant.

Results | A total of 35 819 mother-infant pairs (51% boys) met the study criteria with complete HbA1c and covariate information. The maternal mean (SD) age was 30.9 (5.6) years; the mean (SD) prepregnancy body mass index (calculated as weight in kilograms divided by height in meters squared) was 27.2 (6.4); and 51% were Hispanic, 24%, white, 7%, black, 14%, Asian/Pacific Islander, and 3%, other. The median gestational age at HbA1c testing was 9.0 weeks (interquartile range, 6.7-11.4 weeks); 83% of the testing was in the first trimester. The median HbA1c level was 5.4% (interquartile range, 5.2%-5.6%); 84.9% of pregnancies had HbA1c levels less than 5.7%, 11.7% between 5.7% and 5.9%, 2.4% between 6.0% and 6.5%, and 1% greater than 6.5%. A total of 99% of women with HbA1c levels greater than 6.5% had diabetes during pregnancy (Table footnote “c”).

Children were followed up for a median of 4.5 years (interquartile range, 4.0-5.0 years) after birth, during which time 707 (2.0%) had a clinical diagnosis of ASD. In the multivariable analysis, none of the potential confounders changed the model estimates by more than 10% except for maternal prepregnancy body mass index and race/ethnicity.

<table>
<thead>
<tr>
<th>HbA1c Category</th>
<th>ASD Cases/Total Children, No. (%)</th>
<th>Unadjusted Hazard Ratios (95% CI)</th>
<th>P Value</th>
<th>Adjusted Hazard Ratios (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>As a continuous variable (per 1% increase)</td>
<td>1.23 (1.08-1.41)</td>
<td>.002</td>
<td>1.12 (0.96-1.31)</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>As a categorical variable†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.7%</td>
<td>574/30 419 (1.89)</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>5.7%-5.9%</td>
<td>101/41 72 (2.42)</td>
<td>1.24 (1.01-1.54)</td>
<td>.04</td>
<td>1.08 (0.87-1.35)</td>
<td>.46</td>
</tr>
<tr>
<td>6.0%-6.5%</td>
<td>17/871 (1.95)</td>
<td>0.98 (0.61-1.59)</td>
<td>.94</td>
<td>0.79 (0.48-1.28)</td>
<td>.33</td>
</tr>
<tr>
<td>&gt;6.5%</td>
<td>15/35 7 (4.20)</td>
<td>2.17 (1.30-3.62)</td>
<td>.003</td>
<td>1.79 (1.06-3.00)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: ASD, autism spectrum disorder (includes autistic disorders, Asperger syndrome, or pervasive developmental disorder not otherwise specified); GD, gestational diabetes; HbA1c, hemoglobin A1c; TID, preexisting type 1 diabetes; T2D, preexisting type 2 diabetes.

None of them changed the model estimates by more than 10% except for maternal prepregnancy body mass index and race/ethnicity.

a Estimated by Cox regression models adjusted for maternal race/ethnicity and prepregnancy body mass index (calculated as weight in kilograms divided by height in meters squared).

b Distribution of diabetes status: overall: 0.4% TID, 5.7% T2D, 9.3% GD, and 84.6% no diabetes; for HbA1c greater than 6.5%: 19.9% TID, 70.6% T2D, 8.1% GD, and 1.4% no diabetes; for HbA1c between 6.0% and 6.5%: 2.6% TID, 37.3% T2D, 31.3% GD, and 28.7% no diabetes; for HbA1c between 5.7% and 5.9%: 0.3% TID, 14.2% T2D, 17.4% GD, and 68.1% no diabetes; and for HbA1c less than 5.7%: 0.1% TID, 2.8% T2D, 76.6% GD, and 89.5% no diabetes.

JAMA August 6, 2019 Volume 322, Number 5
After adjusting for these variables, the hazard ratio of ASD associated with each 1% increase of HbA1c level was 1.12 (95% CI, 0.96-1.31; \( P = .15 \)) for the continuous measure and 1.08 (95% CI, 0.87-1.35; \( P = .33 \)) for HbA1c level between 6.0% and 6.5%, and 1.79 (95% CI, 1.06-3.00; \( P = .03 \)) for HbA1c level greater than 6.5% relative to HbA1c level less than 5.7% (Table; Figure). The risk associated with HbA1c levels did not vary by gestational age at HbA1c testing (\( P > .19 \) for interaction).

Discussion | In this study, there was no association between maternal HbA1c levels during early pregnancy and ASD in offspring when HbA1c levels were analyzed as a continuous variable or as a categorical measure if less than 6.5%. An association with HbA1c levels greater than 6.5% was found but was based on only 15 affected children. These findings are consistent with previous observations and the preconception counseling recommendation to optimize glycemic control with HbA1c levels greater than 6.5%.

These results suggest that maternal glycemic control in early pregnancy may be important for ASD risk in offspring. Study limitations include the lack of information on maternal glycemic control throughout pregnancy, other prenatal and early life risk factors, paternal risk factors, and genetic factors as well as the relatively small sample size for pregnancies with HbA1c levels greater than 6.5%.

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Accepted for Publication: May 30, 2019.

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Published Online: June 9, 2019. doi:10.1001/jama.2019.8584

Author Contributions: Dr Xiang and Ms Chow had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Xiang, Buchanan, Feldman.

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Drafting of the manuscript: Xiang.

Critical revision of the manuscript for important intellectual content: All authors.

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Obtained funding: Xiang.

Administrative, technical, or material support: Xiang, Martinez, Page.

Supervision: Xiang.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was partially supported by Kaiser Permanente Southern California Direct Community Benefit funds.

Role of the Funder/Sponsor: The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The opinions expressed are solely the responsibility of the authors and do not necessarily reflect the official views of the Kaiser Permanente Community Benefit Funds.

Meeting Presentation: This study was presented at the American Diabetes Association 79th Scientific Session; June 9, 2019; San Francisco, California.

