The effect of periconceptional folic acid use on embryonic growth of the cerebellum

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AIM: to investigate whether the moment of initiation of periconceptional folic acid (FA) use predicts the growth of the embryonic cerebellum.

Materials & methods

Cerebellar measurements
- Transcerebellar diameter (TCD)
- Left cerebellar diameter (LCD)
- Right cerebellar diameter (RCD)

Datasets
- 8+0 – 12+6 weeks GA

Analysis
- SAS: Linear mixed model analysis
- SPSS: Z-score analysis

Study population

Materials & methods

Folate and the cerebellum

Folate (general and human studies)
- Important in cell cycle regulation, amino acid biosynthesis, protein processing, DNA nucleotide synthesis and methylation
- Prenatal deficiency associated with neural tube defects and congenital anomalies

Brain development (animal studies)
- Folate deficiency in early pregnancy increased apoptosis fetal forebrain, decreased fetal brain weight
- MTHFR deficiency postnatal decreased cerebellar size

Study Design

- Embedded in the Rotterdam Predict study (periconceptional cohort study)
- Inclusion criteria: 18+, informed consent
- Exclusion criteria:
  - Non-viable pregnancies
  - Multiple pregnancies
  - Chromosomal disorders
  - Intra-uterine fetal deaths
  - Major congenital anomalies
  - Pregnancies after oocyte donations
  - Pregnancies dated on CRL
  - Unknown use of folic acid supplements

- Materials:
  - Three-dimensional ultrasound (3D-US) from 6+0 to 12+6 weeks GA
  - Questionnaires

Garel et al, 2011
Larsen, 2001
Carlson, 2004

Folate and the cerebellum

Cerebellum origin

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Population characteristics: pre- vs postconceptional initiation of FA

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 186)</th>
<th>Preconception FA (n=150)</th>
<th>Postconception FA (n=36)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>32.0 (4.8)</td>
<td>32.1 (4.7)</td>
<td>31.6 (5.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Ethnicity*, n (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch</td>
<td>144 (77.8)</td>
<td>125 (83.9)</td>
<td>19 (52.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>Western-other</td>
<td>16 (8.6)</td>
<td>13 (8.7)</td>
<td>3 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Non-western</td>
<td>25 (13.5)</td>
<td>11 (7.4)</td>
<td>14 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Education*, n (%):</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Low</td>
<td>15 (8.1)</td>
<td>13 (8.7)</td>
<td>2 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>62 (33.5)</td>
<td>47 (31.3)</td>
<td>15 (42.9)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>108 (58.4)</td>
<td>90 (60.0)</td>
<td>18 (51.4)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m², median (range)</td>
<td>24.5 (18.6 – 38.3)</td>
<td>24.4 (18.6 – 34.9)</td>
<td>24.9 (19.1 – 38.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Primigravida *, n (%)</td>
<td>69 (37.1)</td>
<td>64 (42.7)</td>
<td>5 (13.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* = range, / = missing

Total cerebellar diameter / CRL and moment of folic acid initiation

Model
1. Univariate
2. Adjusted after stepwise backward elimination. Adjusted for mode of conception, ethnicity, gravidity and their interaction with GA

Preconceptional FA:

<table>
<thead>
<tr>
<th>TCD / CRL</th>
<th>$\beta$ (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preadjusted</td>
<td>-0.08244 (0.02276)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Adjusted</td>
<td>-0.08791 (0.02587)</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

GA Difference in TCD between pre and postconceptional FA initiation

9$^a$ $\pm$ 0.002 (8.2%)
12$^a$ $\pm$ 0.012 (7.0%)

Preconception initiation of FA use is associated with a larger cerebellum, compared to postconception initiation

The first study on the effect of periconceptional folic acid supplements on human cerebellar growth trajectories in the first trimester.

Limitations
- Selected population
- Answers on questionnaires are self-reported
- Relatively low success rate of the cerebellum measurements

Implication
- Is a larger first trimester cerebellum beneficial?

Future
- To compare 1st trimester cerebellar growth to 2nd trimester cerebellar growth.
- To correlate 1st trimester cerebellar growth to birth outcomes.

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