Maternal Use of Acid Reducers Before and During Pregnancy: Trends and Risks for Birth Defects Among Offspring

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What are acid reducers?

- Medications that suppress gastric acid secretion
- Indications: GERD, erosive esophagitis, ulcers and H. pylori infection (w/ antibiotics)

(1) Histamine-2 Receptor Antagonists (H2As)

- Action – block earliest stimuli for acid secretion, histamine
- Less effective than proton pump inhibitors -- H2As faster acting, but shorter duration

Background

Tagamet (cimetidine) 1982
Zantac (ranitidine) 1983
Pepcid (famotidine) 1985
Axid (nizatidine) 1986
H2As go OTC 1995
What are Acid Reducers? (cont’d)

(2) Proton Pump Inhibitors

- Action – block the final step in acid secretion pathway in the stomach; shut down the proton pumps leading greater suppression of acid.
- Delayed onset, but longer acting
Many women may be exposed in early pregnancy
- PPIs and H2As are available OTC as well as via prescription
- Symptoms of gastroesophageal reflux disorders (GERD) are common during pregnancy and may worsen severity of NVP

Data on the safety of acid reducers is limited
- Most studies have shown no significant increase in overall risk of birth defects
- A recent cohort found a modest increase in overall risk following preconceptional exposure to PPIs (Pasternak 2011)
  - Risk of heart defects and urinary tract defects, but were dismissed as chance findings
  - Few studies have evaluated defect-specific effects
Objectives

- To describe trends in acid reducer use among NBDPS participants
- To evaluate whether maternal use of PPIs during the periconceptional period is associated with an increased risk of specific birth defects
- To evaluate whether maternal use of H2As during the periconceptional period is associated with an increased risk of specific birth defects
Methods: Exposure and Outcomes

Exposure

- Primary Comparisons
  - Any PPI use B1-P3 (versus no use B3-P9)
  - Any H2A use B1-P3 (versus no use B3-P9)

- Timing
- Specific medications

Outcomes – NBDPS Defects

- ≥ 200 cases
- ≥ 4 cases exposed during the periconceptional period, B1-P3
Methods: Covariates

- Maternal demographic factors
  - Age
  - Race/ethnicity
  - Education
  - Center

- Behavior and lifestyle factors
  - Maternal smoking
  - Maternal alcohol use
  - MV/FA supplementation

- Reproductive/medical factors
  - Gravidity
  - Pre-pregnancy BMI
  - History of diabetes
  - History of hypertension
  - Periconceptional Infection
Methods: Statistical Analysis

- Logistic regression used to estimate crude and adjusted odds ratios with 95% CIs

- Models adjusted for covariates judged to be both:
  - (1) associated with occurrence of birth defects in at least one organ system
  - (2) associated with exposure among controls
Methods: Statistical Analysis

- Factors associated with periconceptional PPI use
  - White race, age ≥ 25, BMI ≥ 30, higher education, smoking, study center

- Factors associated with periconceptional H2A use
  - White race, age ≥ 25, BMI ≥ 25, higher education, FA/MV use, hypertension, study center

- Cases and Controls differed on:
  - Race, age, BMI, education, study center, alcohol use, FA/MV, hypertension, diabetes
Trends in Maternal Acid Reducer Use
Results: Trends in Acid Reducer Use

Acid Reducer Use Among Mothers in the NBDPS (controls)

H2A Prevalence overall: 1.6%
PPI Prevalence overall: 0.9%

Year of Conception

Exposed Controls (%)

PPIs start to go OTC

Any PPI use
Any H2A use

- 1997-1998
- 1999-2000
- 2001-2002
- 2003-2004
- 2005-2007
Trends in Acid Reducer Use

Maternal H2A Use Before and During Pregnancy

- Preconception
- 1st Trimester
- 2nd/3rd Trimester

Year of Conception:
- 1997-1998
- 1999-2000
- 2001-2002
- 2003-2004
- 2005-2007

Exposed Controls (%)
Trends in Acid Reducer Use

Maternal PPI Use Before and During Pregnancy

- Preconception
- 1st Trimester
- 2nd/3rd Trimester

Year of Conception:
- 1997-1998
- 1999-2000
- 2001-2002
- 2003-2004
- 2005-2007
Results: Trends in H2A Use

Month of PPI Exposure

- Controls
- Cases
- % Difference
Results: Trends in PPI Use

% Exposed

Month of PPI Exposure

Controls  Cases  % Difference

% Difference
Results: Periconceptional Use of Specific H2As

- Ranitidine: 0.40%
- Famotidine: 0.20%
- Cimetidine: 0.10%
- Nizatidine: 0.05%

Controls vs. Cases
Results: Periconceptional Use of Specific PPIs

<table>
<thead>
<tr>
<th>Specific PPI</th>
<th>% Exposed Controls</th>
<th>% Exposed Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole</td>
<td>0.40%</td>
<td>0.50%</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>0.30%</td>
<td>0.30%</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>0.20%</td>
<td>0.16%</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>0.10%</td>
<td>0.10%</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>0.05%</td>
<td>0.10%</td>
</tr>
</tbody>
</table>
Maternal H2A Use and Risk for Specific Birth Defects
### H2A Crude and Adjusted* ORs (95% CIs) – Non-heart Defects

<table>
<thead>
<tr>
<th>Specific Defect</th>
<th>#Exposed / Total</th>
<th>Crude Odds Ratio</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
<td>4 / 407</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spina bifida</td>
<td>8 / 864</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleft palate</td>
<td>10 / 1140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleft lip +/- cleft palate</td>
<td>10 / 2141</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal atresia</td>
<td>5 / 509</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorectal atresia/stenosis</td>
<td>4 / 741</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypospadias 2\textsuperscript{nd}/3\textsuperscript{rd} degree</td>
<td>12 / 1622</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transverse limb deficiency</td>
<td>6 / 493</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>5 / 1030</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omphalocele</td>
<td>4 / 320</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroschisis</td>
<td>4 / 918</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Index: Any H2A Exposure B1-P3,  Reference: No Acid Reducer Exposure B3-P9

*Adjusted for race, age, BMI, education, hypertension, smoking, any FAMV use B1-P3 and study center
H2A Crude and Adjusted* ORs (95% CIs) – Heart Defects

<table>
<thead>
<tr>
<th>Specific Defect</th>
<th>Exposed / Total</th>
<th>Crude</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conotruncal defects</td>
<td>11 / 1823</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>6 / 837</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVOT defects</td>
<td>11 / 1497</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>6 / 786</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVOT defects</td>
<td>16 / 1410</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary valve stenosis</td>
<td>13 / 1036</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal defects</td>
<td>27 / 3737</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD perimembranous</td>
<td>8 / 1453</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASD secundum</td>
<td>11 / 1730</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Index: Any H2A Exposure B1-P3, Reference: No Acid Reducer Exposure B3-P9

*Adjusted for race, age, BMI, education, hypertension, smoking, any FAMV use B1-P3 and study center
Maternal PPI Use and Risk for Specific Birth Defects
Crude and Adjusted* ORs (95% CIs) – Non-heart Defects

<table>
<thead>
<tr>
<th>Defect</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly, 5/439</td>
<td></td>
<td>2.4 (0.9, 6.2)</td>
</tr>
<tr>
<td>Hydrocephaly, 4/387</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleft Palate, 10/1201</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleft lip +/- cleft palate, 9/2274</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal atresia, 9/539</td>
<td>2.7 (1.3, 5.8)</td>
<td>3.1 (1.5, 6.4)</td>
</tr>
<tr>
<td>Hypospadias, 16/1679</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transverse limb deficiency, 6/529</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniosynostosis, 10/1066</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for maternal race, age, BMI, education, hypertension, smoking, FAMV, study center

Index: Any PPI Exposure B1-P3, Reference: No Acid Reducer Exposure B3-P9
Crude and Adjusted* ORs (95% CIs) – Heart Defects

Defect, # exposed/total

Conotruncal defects, 14/1924
Tetralogy of Fallot, 5/882
d-Trans of the great arteries, 5/587
LVOT defects, 12/1579
Hypoplastic left heart, 4/471
Aortic valve stenosis, 5/354
RVOT defects, 10/1493
Pulmonary valve stenosis, 9/1098
Septal defects, 26/3952
VSD perimembranous, 8/1839
ASD secundum, 14/1839
ASD NOS, 4/555

*Adjusted for maternal race, age, BMI, education, history of hypertension, smoking, FAMV, study center

Index: Any PPI Exposure B1-P3 , Reference: No Acid Reducer Exposure B3-P9
## Results: Timing of Exposure to PPIs

### Reference: No Acid Reducer Exposure B3-P9

<table>
<thead>
<tr>
<th>Defect</th>
<th>Any Preconception</th>
<th>1st trimester, no preconception</th>
<th>Preconception &amp; 1st trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, Controls</td>
<td>cOR (CI)</td>
<td>Cases, Controls</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>3, 27</td>
<td>2.3 (0.7, 7.9)</td>
<td>2, 17</td>
</tr>
<tr>
<td>Esophageal Atresia</td>
<td>4, 27</td>
<td>2.1 (0.7, 6.1)</td>
<td>5, 17</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>3, 4</td>
<td>1.9 (0.4, 8.7)</td>
<td>5, 8</td>
</tr>
</tbody>
</table>
## Results: Specific PPIs

### Defects

<table>
<thead>
<tr>
<th>Defect</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Esomeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
<td>--</td>
<td>3/5</td>
<td>3.2 (0.7, 14.4)</td>
</tr>
<tr>
<td></td>
<td>3/9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0 (0.9, 10.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal Atresia</td>
<td>6/16</td>
<td>3.6 (0.9, 14.3)</td>
<td>3/16</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>3/9</td>
<td>5/9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0 (0.9, 9.9)</td>
<td>6.4 (2.2, 18.6)</td>
<td>3.6 (0.9, 14.3)</td>
</tr>
</tbody>
</table>

Reference: No Acid Reducer Exposure B3-P9
Provide further reassurance that acid reducers are not likely major risk factors for birth defects

Some evidence for modest increases in risk for a few specific defects
  - Anencephaly
  - Esophageal atresia
  - Hypospadias
Acknowledgements

- Marlene Anderka, PI

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- Participants