Statistical Analyses

With each study cohort, the prevalences of OC and MCMs were determined as the number of cases divided by the denominator for each group and expressed as a percentage and 95% confidence interval (CI).

To compare the prevalences of these outcomes between the TPM-exposed cohort and the control cohort of infants exposed to OVIRs and their 95% confidence intervals were calculated. Relative risk calculations compared the TPM to AED and TPM to in utero controls.

Results

Patient Demographics

Groups were compared with respect to demographics (Table 1). There were no significant differences in categorical variables of age, gender, race, or ethnicity. The proportion of TPM-exposed infants who were exposed to maternal diabetes mellitus during pregnancy was approximately 9% in the dataset at the whole, with the highest risk in the Epilepsy cohort (approximately 23%). Rates of maternal smoking in the literature are approximately 7% for the total population sample, and there are no significant differences across groups. Because there were no differences, reliability was consistent across groups, these analyses were not removed from individual groups.

Major congenital malformations

Major congenital malformations data across all groups for prevalent oral clefts is provided in Table 2.

Table 3: Frequency of major congenital malformations

<table>
<thead>
<tr>
<th>Dataset Sample</th>
<th>Control</th>
<th>TPM</th>
<th>AED Control</th>
<th>AED</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dataset Sample</td>
<td>100,001</td>
<td>3,961</td>
<td>13,083</td>
<td>36</td>
<td>0.93 (0.23, 3.87)</td>
</tr>
<tr>
<td>Diabetes Control</td>
<td>13,083</td>
<td>36</td>
<td>0.93 (0.23, 3.87)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oral clefts

Data across all groups for prevalent oral clefts is provided in Table 2.

Table 2: Frequency of oral clefts

<table>
<thead>
<tr>
<th>Patients, n</th>
<th># OC</th>
<th>% OC</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dataset Sample</td>
<td>100,001</td>
<td>3,961</td>
<td>13,083</td>
</tr>
<tr>
<td>Diabetes Control</td>
<td>13,083</td>
<td>36</td>
<td>0.93 (0.23, 3.87)</td>
</tr>
</tbody>
</table>

Conclusions

These results do not support a significantly increased risk of oral clefts or major congenital malformations following maternal use of TPM. The risk for MCMs in infants born to diabetic mothers is significantly higher than in the TPM-exposed cohort, although not statistically significant.

The phenotypes seen in the TPM and control groups are comparable and balanced. These results do not support a significantly increased risk of oral clefts or major congenital malformations following maternal use of TPM. The risk for MCMs in infants born to diabetic mothers is significantly higher than in the TPM-exposed cohort, although not statistically significant.

No dose relationship was seen for TPM exposure and MCM or OC risks. The prevalence of OCs and MCMs was similar for all maternal age groups and in the presence or absence of diabetes.

The incidence of OCs and MCMs was determined as 12 months following birth to identify the highest likelihood of malformations occurring. This study used the WO Source® Lx dataset, a claims-based dataset. There is no direct way to verify the presence of oral clefts or major congenital malformations in these claims, but the prevalence rates are similar to those reported in the literature.

The WO Source® Lx dataset is a claims-based dataset. There is no direct way to verify the presence of oral clefts or major congenital malformations in these claims, but the prevalence rates are similar to those reported in the literature.

No dose relationship was seen for TPM exposure and MCM or OC risks. The prevalence of OCs and MCMs was similar for all maternal age groups and in the presence or absence of diabetes.