Original Contribution

Elevated Risk of Preeclampsia in Pregnant Women With Depression: Depression or Antidepressants?

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A previous study suggested an increased risk of preeclampsia among women treated with selective serotonin reuptake inhibitors (SSRIs). Using population-based health-care utilization databases from British Columbia (1997–2006), the authors conducted a study of 69,448 pregnancies in women with depression. They compared risk of preeclampsia in women using SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCAs) between gestational weeks 10 and 20 with risk in depressed women not using antidepressants. Among prepregnancy antidepressant users, the authors compared the risk in women who continued antidepressants between gestational weeks 10 and 24 with the risk in those who discontinued. Relative risks and 95% confidence intervals were estimated. The risk of preeclampsia in depressed women not treated with antidepressants (2.4%) was similar to that in women without depression (2.3%). Compared with women with untreated depression, women treated with SSRI, SNRI, and TCA monotherapy had adjusted relative risks of 1.22 (95% confidence interval: 0.97, 1.54), 1.95 (95% CI: 1.25, 3.03), and 3.23 (95% CI: 1.87, 5.59), respectively. Within prepregnancy antidepressant users, the relative risk for preeclampsia among continuers compared with discontinuers was 1.32 (95% CI: 0.95, 1.84) for SSRI, 3.43 (95% CI: 1.77, 6.65) for SNRI, and 3.26 (95% CI: 1.04, 10.24) for TCA monotherapy. Study results suggest that women who use antidepressants during pregnancy, especially SNRIs and TCAs, have an elevated risk of preeclampsia. These associations may reflect drug effects or more severe depression.

antidepressants; depression; pre-eclampsia; pregnancy

Abbreviations: CI, confidence interval; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Preeclampsia occurs in 2%–4.5% of all pregnancies (1–4) and can seriously compromise maternal and fetal health (5). It has been proposed that preeclampsia is the result of reduced placental perfusion and that genetic, behavioral, and environmental factors can increase the risk for preeclampsia (6). Depression may be one of the conditions that predispose women to preeclampsia. Systemic inflammation and oxidative stress have been proposed as possible factors involved in the pathogenesis of preeclampsia (6, 7), and markers for these processes are increased in individuals with depression (8–10). At least 3 studies have reported an association between depression and preeclampsia (11–13).

However, antidepressants might at least partially explain this association. Between 2% and 13% of pregnant women are treated with antidepressants in the United States (14–16). Selective serotonin reuptake inhibitor (SSRI) antidepressants inhibit serotonin reuptake, and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants and tricyclic antidepressants (TCA) inhibit serotonin and norepinephrine reuptake to varying degrees (17, 18). Increased serotonin and norepinephrine levels may contribute to the development of preeclampsia (19, 20). Toh et al. (21) reported that pregnant women who continued SSRI treatment after the first trimester had an increased risk for preeclampsia compared with those...
who were not exposed, while those who discontinued had no increased risk. Reis and Kallen (22) reported an increased risk for preeclampsia among women who used any antidepressants during pregnancy. It remains unclear whether the observed association between antidepressants and preeclampsia is due to the antidepressants or to underlying mood disorders.

Given the large number of pregnant women who are treated with antidepressants, it is critical to determine whether the treatment impacts the risk for preeclampsia and, if so, whether a potential effect varies among types of antidepressants or by timing of use. Using health-care utilization databases from British Columbia, we compared the risk for preeclampsia among women with depression by SSRI, SNRI, and TCA use during pregnancy and by continuation versus discontinuation of these antidepressants after 10 gestational weeks.

MATERIALS AND METHODS

Data source

Comprehensive health insurance is provided to nearly all residents of British Columbia (23). We used province-wide health-care utilization databases that were compiled by the British Columbia Ministry of Health to identify pregnant women and newborns. These population-based databases, which contain diagnostic and procedural information from all physician services and hospitalizations, were linked to the PharmaNet database, which contains all non-hospital pharmacy dispensings. This study was approved by the Brigham and Women’s Hospital Institutional Review Board, and signed data use agreements were in place.

Women were linked to infants by family insurance number and by delivery month and year. The delivery date was estimated from the inpatient delivery discharges. Women who had more than one infant with the same delivery date were identified as having a multifetal gestation. Of all identified deliveries, 94% were linked to infants. Because neither gestational length nor date of the last menstrual period is available in administrative databases, the date of the last menstrual period was assigned as 280 days prior to the estimated delivery date, the mean duration of human gestation (24).

Cohort definition

Only pregnancies that ended in a livebirth between October 1, 1997, and January 31, 2006, and in which women had continuous health-care enrollment from 1 year prior to the last menstrual period until 2 months after their delivery date were eligible (306,831 pregnancies from 224,827 women). To minimize confounding by depression, we restricted the cohort to women with at least 1 inpatient or outpatient code for depression during the year prior to the last menstrual period until 20 completed gestational weeks. Depression was defined as International Classification of Diseases, Ninth Revision (ICD-9), codes 296.x, 300.x, 309.x, 311.x; as International Classification of Diseases, Tenth Revision (ICD-10), codes F30.x–F39.x and F40.x–F48.x; or as a British Columbia–specific outpatient code, “anxiety/depression.” West et al. (25) reported that the positive predictive value of these outpatient ICD-9 codes to identify depression among antidepressant users in the Saskatchewan Health administrative databases was 77%; most of the individuals labeled as false positives had other mental health diagnoses, including anxiety.

Exposure definitions

Antidepressant use/exposure was determined by the presence of at least 1 pharmacy dispensing record for an SSRI, SNRI, TCA, or “other antidepressant” during estimated gestational weeks 10–20. Exposure was classified as mono-therapy if dispensings for only 1 antidepressant class were present during pregnancy and as polytherapy otherwise. The “other antidepressant” group was not explored in the analyses because of small size. Venlafaxine was the only SNRI present in the database. Bupropion was not included because it was marketed for smoking cessation. Women with no antidepressant dispensings between the year prior to the last menstrual period and gestational week 20 were classified as having no antidepressant use, even if an antidepressant was dispensed after week 20.

We selected an exposure window between gestational weeks 10 and 20 (Figure 1) because we hypothesize that antidepressants may impact preeclampsia risk when used after the first trimester of pregnancy on the basis of the results of Toh et al. (21). Furthermore, we set the exposure window to end just before preeclampsia can be diagnosed, by definition, to avoid potential reverse causation. Women with a depression diagnosis before gestational week 10 and at least 1 dispensing for only SSRIs, SNRIs, or TCAs during the 3 months prior to the last menstrual period and no dispensings for another class of antidepressants during pregnancy were eligible for continuation/discontinuation exposure classification. These women were classified as discontinuers if they had no antidepressant dispensing or days’ supply between gestational weeks 10 and 24 and as continuers if they did have a dispensing between weeks 10 and 24. The small proportion of women who resumed treatment after 24 weeks were classified as discontinuers. We limited the continuation window to 24 weeks because the opportunity to continue antidepressants during the third trimester would be lower in women with preeclampsia, since they have a higher risk of preterm deliveries (26, 27).

Outcome assessment

Preeclampsia was defined as hypertension and proteinuria occurring after the 20th week of gestation (28). We identified cases by the presence of at least 1 of the following inpatient or outpatient ICD-9 codes 642.4x, 642.5x, 642.6x, or 642.7x or ICD-10 codes O11.x, O14.x, or O15.x between gestational week 20 and 1 month after delivery. Most cases of preeclampsia were identified with at least 1 inpatient code for the condition (93.8%). The positive predictive value for specific forms of preeclampsia and eclampsia ranged from 41.7% to 84.8% in a validation study of ICD-9 hospital discharge codes (29), and the positive predictive value for preeclampsia based on ICD-9 codes for mild and severe disease was 93% in the Swedish Medical Birth Register (30).
Covariates

We captured information on women’s characteristics during a baseline period that began 1 year prior to the last menstrual period and ended at 10 gestational weeks. Potential confounders included established risk factors for preeclampsia and factors related to depression severity during the baseline: age (as a quadratic spline), primiparity (no prior deliveries recorded in the database for a woman; multiparas are identified only when prior deliveries are recorded), multifetal gestation, diabetes, obesity, renal disease, number of depression claims (up to 20 gestational weeks), other mental health disorders, a binary composite of other antidepressant indications (sleep disorders, migraine, or other pain-related conditions: fibromyalgia, rheumatoid arthritis, inflammatory bowel disease, or gastrointestinal ulcers) (definitions in Web Table 1, the first of 4 Web tables and a Web Appendix posted to the Journal’s website (http://aje.oxfordjournals.org/)), number of psychiatrist visits and mental health hospitalizations, and dispensings for benzodiazepines, antipsychotics, and anticonvulsants (binary variables). The number of distinct prescription drugs excluding antidepressants, physician visits (<10, 10–19, 20–29, ≥30), and non-mental health hospitalizations during the baseline were considered as markers of comorbidity (31). The number of antidepressant classes and the total days’ supply of all antidepressant dispensings (<90, 90–364, ≥365) during the year before the last menstrual period were used to capture antidepressant history.

Statistical analysis

Antidepressant use was described among all eligible pregnancies (Web Appendix). Three primary analyses estimated the risk for preeclampsia and compared it among different exposure groups. 1) In the main analysis, to assess the risk for preeclampsia by antidepressant use versus non-use, we compared women who used antidepressants between weeks 10 and 20 with women with no antidepressant use. 2) In the comparative safety analysis, to assess the risk for preeclampsia among antidepressant users by class, we compared the SSRI polytherapy group and the SNRI and TCA monotherapy groups with the SSRI monotherapy group. 3) Finally, in the continuation/discontinuation analysis, to assess the risk for preeclampsia by antidepressant continuation versus discontinuation during pregnancy, we compared SSRI, SNRI, and TCA monotherapy continuers with discontinuers.

Logistic regression models were used to estimate relative risks and 95% confidence intervals. All models were adjusted for delivery year, and robust variances accounted for correlations among women with multiple pregnancies (32). We included covariates in our models that were associated with the outcome, regardless of statistical significance. Model 1 was adjusted for delivery year. Model 2 was additionally adjusted for preeclampsia risk factors and physician visits, model 3 for depression severity proxies, and model 4 for preeclampsia risk factors, physician visits, and depression severity proxies.

Sensitivity and exploratory analyses

We assessed the sensitivity of the results to a shorter gestational length in preterm deliveries. The last menstrual period was reassigned to be 245 days prior to delivery for preterm deliveries (identified from ICD-9 codes 644.0, 644.2, or 765.x or ICD-10 codes P05.x, P07.x, or O60.1). This method accurately classifies gestational age within 2 weeks for nearly 70% of in-hospital preterm deliveries in this database (33). In addition, we excluded preterm deliveries and performed a subanalysis among term deliveries (≥37 weeks) only; the preterm delivery codes have a negative predictive value of 99.3% in this database (33). We also assessed the sensitivity of the results from the main analysis to changes in the definition of depression (excluding the British Columbia-specific outpatient code “anxiety/depression” from the definition), exposure (assuming full compliance with days’ supply rather than by the date the antidepressant was dispensed, and considering women to be exposed only if they used antidepressants throughout pregnancy as determined by dispensing date and days’ supply plus 14-day grace periods between dispensings), and outcome (inpatient codes only, severe preeclampsia/eclampsia only, and exclusion of women with superimposed preeclampsia).

Preexisting hypertension is a strong risk factor for preeclampsia (34), and SNRI use can elevate blood pressure (35). We explored the role of baseline hypertension by model.
adjustment for both hypertension diagnosis and antihypertensive drug dispensings and by restriction. We also restricted to women without major risk factors for preeclampsia (i.e., diabetes, hypertension, multifetal pregnancies, obesity, and renal disease). We explored the role of timing of exposure among all eligible pregnancies by estimating the relative risk of preeclampsia associated with antidepressant use at different gestational periods; women who had not had antidepressant dispensings until that time were the reference group.

Results from the following exploratory analyses are reported in the Web Appendix. We assessed the risk for preeclampsia by antidepressant dose between weeks 10 and 20; because of small group size, no dose analysis for TCAs was performed.

The SSRI high/low dose definition varied for each SSRI; the SNRI dose cutoff was <150 mg/day. We explored the association between specific SSRIs (fluvoxamine, paroxetine, sertraline, fluoxetine, and citalopram) and preeclampsia among women in the SSRI monotherapy group. We explored effect modification by baseline benzodiazepine use. All analyses were conducted with SAS, version 9.2, for Windows (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The risk of preeclampsia was 2.3% in women without depression and 2.4% in women with depression but no...
Table 1. Baseline Characteristics (Assessed in the Year Before the Last Menstrual Period Until Gestational Week 10) of 69,448 Pregnancies in Which Women Had Diagnosed Depression, According to Exposure Status, British Columbia Health-Care Utilization Data, 1997–2006

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SSRI Monotherapy (n = 3,169)</th>
<th>SSRI Polytherapy (n = 333)</th>
<th>SNRI Monotherapy (n = 408)</th>
<th>TCA Monotherapy (n = 146)</th>
<th>No Antidepressant Therapy (n = 65,392)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>Median (IQR Range)</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Delivery year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997–2000</td>
<td>743</td>
<td>23.5</td>
<td>76 (22.8)</td>
<td>38</td>
<td>9.3</td>
</tr>
<tr>
<td>2001–2003</td>
<td>1,373</td>
<td>43.3</td>
<td>143 (42.9)</td>
<td>154</td>
<td>37.8</td>
</tr>
<tr>
<td>2004–2006</td>
<td>1,053</td>
<td>33.2</td>
<td>114 (34.2)</td>
<td>216</td>
<td>52.9</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997–2000</td>
<td>31</td>
<td>(8)</td>
<td>31 (8)</td>
<td>30</td>
<td>(7)</td>
</tr>
<tr>
<td>2001–2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primiparity</td>
<td>1,941</td>
<td>61.3</td>
<td>197 (59.2)</td>
<td>252</td>
<td>61.8</td>
</tr>
<tr>
<td>Multifetal gestation</td>
<td>33</td>
<td>1.0</td>
<td>8 (2.4)</td>
<td>7</td>
<td>1.7</td>
</tr>
<tr>
<td>Hypertension (diagnosis and antihypertensives)</td>
<td>40</td>
<td>1.3</td>
<td>6 (1.8)</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36</td>
<td>1.1</td>
<td>9 (2.7)</td>
<td>5</td>
<td>1.2</td>
</tr>
<tr>
<td>Obesity</td>
<td>66</td>
<td>2.1</td>
<td>14 (4.2)</td>
<td>8</td>
<td>2.0</td>
</tr>
<tr>
<td>Physician visits, no.</td>
<td>17</td>
<td>(15)</td>
<td>26 (24)</td>
<td>19</td>
<td>(15.5)</td>
</tr>
<tr>
<td>Psychiatrist visits and mental health hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,395 No psychiatric visits and no mental health hospitalizations</td>
<td>2,395</td>
<td>75.6</td>
<td>178 (53.5)</td>
<td>297</td>
<td>72.8</td>
</tr>
<tr>
<td>394 1–4 psychiatric visits and no mental health hospitalizations</td>
<td>394</td>
<td>12.4</td>
<td>59 (17.7)</td>
<td>55</td>
<td>13.5</td>
</tr>
<tr>
<td>232 ≥5 psychiatric visits and no mental health hospitalizations</td>
<td>232</td>
<td>7.3</td>
<td>45 (13.5)</td>
<td>33</td>
<td>8.1</td>
</tr>
<tr>
<td>148 &gt;1 or more mental health hospitalizations</td>
<td>148</td>
<td>4.7</td>
<td>51 (15.3)</td>
<td>23</td>
<td>5.6</td>
</tr>
<tr>
<td>Depression claims up to gestational week 20, no.</td>
<td>4</td>
<td>(5)</td>
<td>8 (11)</td>
<td>5</td>
<td>(6)</td>
</tr>
<tr>
<td>Anticonvulsant dispensing</td>
<td>114</td>
<td>3.6</td>
<td>39 (11.7)</td>
<td>22</td>
<td>5.4</td>
</tr>
<tr>
<td>Antipsychotic dispensing</td>
<td>118</td>
<td>3.7</td>
<td>41 (12.3)</td>
<td>19</td>
<td>4.7</td>
</tr>
<tr>
<td>Benzodiazepine dispensing</td>
<td>870</td>
<td>27.5</td>
<td>165 (49.6)</td>
<td>125</td>
<td>30.6</td>
</tr>
<tr>
<td>Other mental health disorder</td>
<td>301</td>
<td>9.5</td>
<td>71 (21.3)</td>
<td>43</td>
<td>10.5</td>
</tr>
<tr>
<td>Sleep disorders, migraine, or other pain-related conditions</td>
<td>263</td>
<td>8.3</td>
<td>51 (15.3)</td>
<td>30</td>
<td>7.4</td>
</tr>
<tr>
<td>Total antidepressant days’ supply in the year before the last menstrual period</td>
<td>240  (234)</td>
<td></td>
<td>345 (344)</td>
<td>299 (231.5)</td>
<td>265.5 (310)</td>
</tr>
<tr>
<td>No. of antidepressant classes used in the year before the last menstrual period</td>
<td>403</td>
<td>12.7</td>
<td>27 (8.1)</td>
<td>22</td>
<td>5.4</td>
</tr>
<tr>
<td>1</td>
<td>2,435</td>
<td>76.8</td>
<td>110 (33.0)</td>
<td>295</td>
<td>72.3</td>
</tr>
<tr>
<td>2</td>
<td>294</td>
<td>9.3</td>
<td>157 (47.2)</td>
<td>85</td>
<td>20.8</td>
</tr>
<tr>
<td>3–4</td>
<td>37</td>
<td>1.2</td>
<td>39 (11.7)</td>
<td>6</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
antidepressant dispensions. Pregnancies in which women had depression and were treated with antidepressants between weeks 10 and 20 had a higher risk for preeclampsia (Figure 2A). Baseline characteristics of 69,448 pregnancies in women with depression are reported in Table 1. The antidepressant-exposed groups had more depression claims and more psychiatric visits/mental health hospitalizations than did women without antidepressant dispensions. Among women with depression, a higher number of depression claims, benzodiazepine use, and psychiatrist visits/mental health hospitalizations was associated with a higher risk of preeclampsia, even when adjusting for antidepressants.

Although adjustment for preeclampsia risk factors and physician visits (model 2) did not substantially alter the relative risk estimates from the delivery year-adjusted model (model 1), additional adjustment for depression severity proxies (model 4) attenuated the relative risks for specific antidepressant classes (Table 2). Compared with the risk for no antidepressant use, the fully adjusted relative risks were 1.22 (95% confidence interval (CI): 0.97, 1.54) for SSRI, 1.95 (95% CI: 1.25, 3.03) for SNRI, and 3.23 (95% CI: 1.87, 5.59) for TCA monotherapies.

Compared with SSRIs in monotherapy, the fully adjusted relative risk for preeclampsia was 0.89 (95% CI: 0.48, 1.63) for SSRI polytherapy, 1.59 (95% CI: 0.99, 2.55) for SNRI monotherapy, and 2.58 (95% CI: 1.40, 4.73) for TCA monotherapy.

The risk for preeclampsia appeared to be higher in antidepressant continuers than in discontinuers (Figure 2B). Comparing continuers with discontinuers, the fully adjusted

<table>
<thead>
<tr>
<th>Exposure Group</th>
<th>No.</th>
<th>Preeclampsia, %</th>
<th>Model 1 RR</th>
<th>95% CI</th>
<th>Model 2 RR</th>
<th>95% CI</th>
<th>Model 3 RR</th>
<th>95% CI</th>
<th>Model 4 RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation</td>
<td>2,561</td>
<td>3.4</td>
<td>1.45</td>
<td>1.06, 1.98</td>
<td>1.42</td>
<td>1.04, 1.95</td>
<td>1.31</td>
<td>0.94, 1.83</td>
<td>1.32</td>
<td>0.95, 1.84</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>3,211</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SNRI monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Continuation</td>
<td>361</td>
<td>7.5</td>
<td>3.30</td>
<td>1.69, 6.47</td>
<td>3.66</td>
<td>1.81, 7.38</td>
<td>2.89</td>
<td>1.54, 5.42</td>
<td>3.43</td>
<td>1.77, 6.65</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>518</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCA monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation</td>
<td>100</td>
<td>13.0</td>
<td>3.60</td>
<td>1.66, 7.81</td>
<td>3.16</td>
<td>1.39, 7.16</td>
<td>3.41</td>
<td>1.20, 9.74</td>
<td>3.26</td>
<td>1.04, 10.24</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>412</td>
<td>3.9</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.


b Model 2: adjusted for delivery year, age, diabetes, multifetal gestation, obesity, primiparity, and physician visits (0–14, 15–30, >30).

c Model 3: adjusted for delivery year, number of depression claims, number of psychiatrist visits/mental health hospitalizations, dispensing of benzodiazepines, total antidepressant days’ supply, and number of antidepressant classes (1 or ≥2).

d Model 4: adjusted for covariates in model 2 and model 3.

e Not adjusted for diabetes.
relative risk for preeclampsia was 1.32 (95% CI: 0.95, 1.84) for SSRI, 3.43 (95% CI: 1.77, 6.65) for SNRI, and 3.26 (95% CI: 1.04, 10.24) for TCA monotherapies (Table 3).

Gestational length, depression, and outcome sensitivity analyses yielded estimates similar to that of the primary analysis, with the exception of the SSRI monotherapy and severe preeclampsia/eclampsia association, which was null. Some associations were attenuated slightly when antidepressant use was classified while assuming full compliance, and the associations were stronger when the exposure was defined as continuous use throughout pregnancy. The results did not change meaningfully with baseline hypertension adjustment or restriction or when the cohort was restricted to pregnancies without major preeclampsia risk factors. (Web Tables 2–4).

The associations between antidepressant use during various gestational time periods and preeclampsia are depicted in Figure 3 for all eligible pregnancies. The SNRI and TCA relative risks were highest in the periods beyond 2 months after the last menstrual period, while the SSRI relative risks were relatively flat around the last menstrual period.

DISCUSSION

We found that women with depression diagnoses who had antidepressant dispensings between gestational weeks 10 and 20 had a higher risk for preeclampsia than did women with depression but no dispensings. Use of SNRIs or TCAs was associated with a 2- and 3-fold increased risk of preeclampsia, respectively. The association between SSRI use and preeclampsia was modest after adjustment for depression severity proxies.

Although having a depression diagnosis was not associated with preeclampsia, depression severity might be and could partially explain the increased risk among women who continue their antidepressants during pregnancy. A variety of mechanisms through which depression may cause preeclampsia have been proposed (11–13). We used several methods to control for potential confounding by depression severity. First, we restricted the cohort to women with depression and adjusted for proxies for depression severity. Similar proxies were used to reduce confounding in a study of antidepressant use and suicide risk (36). Adjustment for depression severity proxies attenuated the relative risk estimates for antidepressants, but it did not annul those for SNRIs and TCAs. Second, the comparative safety and continuation/discontinuation analyses were intended to further reduce confounding by yielding more homogeneous comparisons (37). In addition, these analyses answer the most relevant clinical question: Can preeclampsia risk be decreased by prescribing specific antidepressant classes or by discontinuing antidepressants early in pregnancy? We found that both SSRI monotherapy and antidepressant discontinuation early in pregnancy were associated with a lower risk of preeclampsia than other treatment patterns were. It is possible that antidepressants affect preeclampsia risk through type and degree of monoamine reuptake inhibition and therefore through altered extracellular monoamine concentrations. In vitro studies demonstrated that serotonin increased placental chorionic vein and umbilical artery vasoconstriction (38–40), and in pregnant sheep, uterine artery blood flow and fetal oxygenation transiently decreased after fluoxetine (an SSRI) infusion (41). Norepinephrine caused vasoconstriction in uterine vascular beds from rats (42). Reduced placental blood circulation is an underlying factor in the development of preeclampsia (43); perhaps the effects of increased extracellular serotonin and norepinephrine levels in the placenta contribute to preeclampsia. Venlafaxine behaves as an SSRI at low doses and as an SNRI at doses ≥150 mg (44, 45). Although exploratory, an increased risk was observed in the SNRI high-dose group but not in the low-dose group. TCAs bind to a number of other receptors including muscarinic, cholinergic, histamine H1, and α1-adrenergic receptors (46), which might play an etiologic role.

Depression is a complex condition, and the degree of illness severity can only be approximated with health-care utilization data. Pregnant women who continue antidepressant use or use non-SSRIs or polytherapy may have a higher risk for preeclampsia, because these patterns may indicate more severe depression. Individuals with no or partial response to SSRIs, the first-line therapy for depression (47, 48), may switch to another class of antidepressants or may be treated with combination therapy (48, 49). Improved adjustment for depression severity could have moved the relative risks closer to the null.

Considering the numerous side effects of TCAs (50), perhaps prescription of these antidepressants during pregnancy is a marker for suboptimal health care that is responsible for the increased risk of preeclampsia among women using TCAs.

Women with more severe depression may be diagnosed with preeclampsia because of more frequent health-care contact; however, adjustment for physician visits attenuated the...
results only slightly. Women who take antidepressants may have an underlying phenotype of poor health, and residual confounding by factors related to this phenotype could explain the results. However, neither adjustment nor restriction for known preeclampsia risk factors changed the results materially. Had factors that are positively associated with both antidepressant use and preeclampsia (perhaps prior preeclampsia, prepregnancy body mass index, diabetes) been available or more accurately measured in our data, the adjusted estimates would potentially move further toward the null. Because smoking is inversely and modestly associated with preeclampsia (51), but positively associated with antidepressant use (52), adjustment for smoking would have likely moved results slightly away from the null. However, in Toh et al. (21), adjustment for measured confounders (such as number of fetuses, gravidity, diabetes, smoking, race, and prepregnancy body mass index) had a limited impact on the estimates. For an unmeasured confounder to explain the results, it would have to be strongly associated with the exposure and outcome, and it would need to be fairly prevalent in the study population (53). Although prepregnancy blood pressure was not available, adjustment for baseline hypertension and restriction to those without hypertension slightly attenuated some of the results. Exclusion of women with superimposed preeclampsia attenuated the SSRI associations. It is unclear whether the increased risk of preeclampsia among antidepressant users was partially due to an effect of prepregnancy antidepressant treatment on blood pressure.

A timing analysis supported the hypothesis of an exposure-sensitive window between gestational weeks 10 and 20. It is unclear whether this pattern reveals an etiologically relevant antidepressant exposure window, or if it reflects selection as pregnant women who continue SNRIs and TCAs may have more severe depression. If precise information on gestational age at delivery and at preeclampsia onset were available, then we could have conducted more detailed analyses on the role of exposure timing and continuation/discontinuation during the third trimester. Exposure assessment was based on prescription fills; we could not verify that women were taking the medications (54–57). Sensitivity analyses in which we determined exposure status with days’ supply (i.e., assuming compliance with the last prescription) resulted in some weaker associations. Misidentification of the last menstrual period by assuming 280-day pregnancies would also result in exposure misclassification, particularly among women with preeclampsia, because preeclampsia is associated with preterm delivery (26, 27). Specifically, a spurious association would result from the overestimation of early pregnancy exposure to drugs that are discontinued before conception among women with preterm deliveries. However, the relatively long duration of antidepressant therapy typical in depression treatment and the wide exposure window beginning at 10 weeks would tend to minimize this source of misclassification (58). In fact, the gestational length and term-restricted sensitivity analyses suggested results similar to those from the original analysis. We observed stronger associations when exposure was defined as antidepressant use throughout pregnancy. This exposure is not affected by last menstrual period misclassification, and it is less likely affected by nonadherence; however, it may be associated with depression severity.

Differential outcome misclassification could occur if factors associated with clinician antidepressant prescription preferences were also associated with the accuracy and coding of preeclampsia diagnoses; this could bias the results away from the null. However, a number of findings support the validity of our outcome definition. First, the incidence of preeclampsia in our study was similar to that reported in the literature (1–2, 4). The risk for preeclampsia was higher among pregnancies with the established preeclampsia risk factors (i.e., multifetal gestations, primiparity, obesity, and diabetes) (34). Finally, the results were not very sensitive to alternative outcome definitions.

The study by Toh et al. (21) suggested a stronger relation between SSRI use and preeclampsia than ours; there are many potential explanations. Their study was the first to suggest the association, and the number of exposed women was small (59). It utilized retrospectively self-reported real use of antidepressants rather than dispensings and self-reported preeclampsia. Greater exposure misclassification may have biased our results toward the null, while differential exposure misclassification may have biased their results away from the null. Their results may have been attenuated had they adjusted for depression severity. The study cohort in Toh et al. comprised healthy volunteers, whereas ours was population based; therefore, discrepant population characteristics might also explain the results.

In conclusion, the risk for preeclampsia was elevated among women who were treated with antidepressants; specifically, it was highest among women who were treated with non-SSRI antidepressants after gestational week 10. The relation may reflect drug effects; however, residual confounding by depression severity could not be ruled out. Discontinuation of antidepressants during pregnancy may cause depressive relapse (60). Therefore, it is vital for women who are considering antidepressant discontinuation during pregnancy to balance the potential risks of antidepressant treatment and the harmful effects of untreated depression and depressive relapse on maternal and offspring health (61). Regardless of the reason for the association, women who use antidepressants during pregnancy, especially SNRIs and TCAs, may have an elevated risk for preeclampsia.

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