Gestational Exposure to Antidepressants and Risk of Seizure in Offspring: A Systematic Review and Meta-Analysis

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Background:
- Depression is one of the most common complications during pregnancy
- In the United States, 10% of pregnant women use antidepressants (AD)
- Untreated maternal depression is associated with higher risk of developing post-partum depression and suicidality.
- It is crucial to gather more knowledge on safe AD use as previous reviews suggest an association between gestational AD use and the risk of seizure in offspring.

Objective:
- To summarise the available evidence on the association between gestational antidepressant exposure and the risk of seizure in neonates and children.

Data sources:
- Literature search conducted in PubMed, EMBASE and PsycINFO up to 15th January 2020.
- Search terms used: (Pregnancy AND (Antidepressants) AND (Offspring) AND ((Seizure) OR (Convulsion) OR (Epilepsy))).

Methods:
- All observational studies of case-control, cohort studies and cross-sectional studies, which investigated the association between antidepressants use during pregnancy and seizures or epilepsies in the offspring were included.
- The Newcastle-Ottawa Scale (NOS) was adopted to assess the methodological quality of the included studies.
- 16 studies were included in the review and 13 in the meta-analysis.
- All the studies were published after 2000.

Results:
- A total of 2,105,071 births from 13 studies across 7 countries were included in the meta-analyses.
- All studies retrieved information on antidepressant exposure from secure medical charts.
- Seven studies reported a significant increase in the risk of seizures in offspring while 6 others reported no significant differences.
- The risk of seizures was significantly higher in offspring exposed to maternal antidepressants (pooled RR, 2.30; 95% CI, 1.63-3.24).

Table 1. Name of studies and countries they were conducted in.

<table>
<thead>
<tr>
<th>Country</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Boucher et al. 2008; Oberlander et al. 2006, 2008; Warburton et al. 2010; Wen et al. 2006</td>
</tr>
<tr>
<td>United States</td>
<td>Davis et al. 2007; Hayes et al. 2012; Simon, Cunningham, and Davis 2002</td>
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<tr>
<td>Israel</td>
<td>Leibovitch et al. 2013; Levinson-Castiel et al. 2006</td>
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<tr>
<td>Italy</td>
<td>Bellissima et al. 2020; Cantarutti et al. 2017</td>
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<tr>
<td>Sweden</td>
<td>Kallen 2004a; Lennestal and Kallen 2007</td>
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<tr>
<td>Australia</td>
<td>Galbally et al. 2009</td>
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<tr>
<td>Denmark</td>
<td>Mao et al 2016</td>
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Discussion:
- Gestational antidepressant exposure is associated with a 2.3-fold higher incidence of seizure in offspring.
- No difference in the risk was found from those exposed to other antidepressants in general or more specifically SSRIs.
- Withdrawal of antidepressants in neonates may play a role in seizures in offspring, however this is only part of the explanation.
- Risk of seizures in offspring beyond the neonatal period could possibly be due to the direct action on foetal development that exposure to ADs in pregnancy has.
- Due to the limited number of studies focusing beyond the neonatal period, more studies on long-term risk of seizure in offspring are needed.
- Clinicians should weigh the risks and benefits when considering the continuation or withdrawal of ADs during pregnancy, and the decision ought to be individualised for each patient.

Conclusion:
- Our systematic review and meta-analysis showed an increased risk of seizure in neonates and children of mothers treated with antidepressants during pregnancy. However, the exact causality relationship is yet to be confirmed.