Prenatal exposure to antidepressants or antipsychotics and the risk of seizure in children

Perinatal mental health problems account for a substantial health burden across the world. Almost one in two young women report some form of common mental disorders during pregnancy[1]. The use of psychotropic medications, especially antidepressants and antipsychotics, has doubled in the past two decades, with a disproportionate increase amongst women at childbearing age and during pregnancy[2,3].

Despite increased prescribing, there is insufficient evidence supporting the safety of psychotropic drug use during pregnancy[1], in particular regarding seizure in offspring, one of the most common neurological conditions in early childhood and an important predictor of mortality, long-term disability, and poor prognosis[4]. This may lead to hesitations in perinatal psychiatric treatment: indeed, high rates of discontinuation of psychotropic medications have been observed in pregnant women with mental disorders[5,6]. There can be significant adverse effects to both maternal and foetal health when stopping medications abruptly or withholding treatment during pregnancy[5,6].

We used the Hong Kong Clinical Data Analysis and Reporting System (CDARS)[7] to examine the risk of seizure in offspring (ICD-9-CM diagnosis codes 333, 345, 779 and 780, with the exception of febrile convulsion, ICD-9-CM codes 780.31 and 780.32) associated with prenatal exposure to an antidepressant (British National Formulary, BNF chapter 4.3) or an antipsychotic medication (BNF chapter 4.2.1). We included all pregnant women aged 15-50 years who delivered a live birth between January 1, 2001 and December 31, 2015. All children had at least one-year follow-up by the end of the study period (December 31, 2016). Children without valid mother-child linkage or with incomplete birth information were excluded.

Children were considered as exposed prenatally if their mothers received any antidepressant or antipsychotic medication during the pregnancy period ("maternal gestational use"). Separate exposure cohorts were created for antidepressant and antipsychotic use. Mothers with epilepsy or prenatal lithium treatment may have an increased risk of having a child with seizure[8]; we therefore excluded pregnant women who had a diagnosis of epilepsy, and those treated with lithium during pregnancy. We also excluded mothers with antipsychotic or antidepressant prescriptions in the analyses of antidepressants or antipsychotics, respectively. We restricted the analyses to mothers who received at least two prescriptions of interest.

Based on maternal antidepressant/antipsychotic use in different risk periods, we classified the children into three comparator groups: a) those whose mothers did not use antidepressants/antipsychotics during pregnancy ("maternal gestational non-use"); b) those whose mothers used these drugs any time before pregnancy but stopped treatment when pregnant ("maternal past use"); and c) those whose mothers had never used the drugs before and during pregnancy ("maternal non-use ever"), who were further classified into those with psychiatric disorders (ICD-9-CM codes 290-319) and those without psychiatric disorders.

To explore the impact of confounding by indication, we compared children with "maternal past use" to those with "maternal non-use ever". An increased risk of seizure among children with "maternal past use" indicates confounding by indication, as the infant was not exposed to antidepressants/antipsychotics. Similarly, children with "maternal gestational use" were compared to children with "maternal past use". Secondly, to evaluate the role of maternal psychiatric disorders, we restricted comparison cohorts to children with "maternal non-use ever".

Sibling-matched analysis was conducted to control for shared genetic and social confounding at the family level. Covariates for confounding adjustment were maternal age at delivery, calendar year at delivery, birth hospital, infant gender, parity, maternal underlying medical conditions and socioeconomic status. Cox proportional hazard regression models

with propensity score fine-stratification weighting[9] was used to estimate the hazard ratios with a 95% confidence interval (CI) to assess the association.

This study included 412,796 and 410,587 pairs of mother-child records in the antidepressant and antipsychotic analyses, with a mean follow-up time of 6.59±3.91 and 6.60±3.91 years, respectively. For antidepressants, the proportion of children diagnosed with seizure among those with "maternal gestational use" and "maternal gestational non-use" was 6.75% and 4.46%, respectively. For antipsychotics, the corresponding figures were 9.31% and 4.46%.

Thus, the prenatal use of antidepressants and antipsychotics was associated, respectively, with a 23% (propensity score weighted hazard ratio, wHR=1.23, 95% CI: 1.02-1.48) and 49% (wHR=1.49, 95% CI: 1.11-1.99) increased risk of seizure in children, when compared with unexposed children. However, the increased risk was not observed when children with "maternal gestational use" were compared to those with "maternal past use" (wHR=1.01, 95% CI: 0.79-1.28 for antidepressants; wHR=0.98, 95% CI: 0.64-1.50 for antipsychotics) and with "maternal non-use ever" (wHR=1.13, 95% CI: 0.88-1.44 for antidepressants; wHR=1.32, 95% CI: 0.93-1.89 for antipsychotics).

Moreover, when the analyses were restricted to children with "maternal non-use ever" of antidepressants or antipsychotics, the risk of seizure was consistently higher in children whose mothers had a psychiatric disorder, compared to those whose mothers had no psychiatric disorder (wHR=1.44, 95% CI: 1.25-1.67 for antidepressants; wHR=1.41, 95% CI: 1.20-1.66 for antipsychotics). Comparisons between children with "maternal gestational use" and the sibling-matched children with "maternal gestational non-use" also showed no statistically significant difference (wHR=1.16, 95% CI: 0.75-1.77 for antidepressants; wHR=1.19, 95% CI: 0.29-4.82 for antipsychotics).

The results of our study, therefore, do not support a causal relationship between prenatal exposure to antidepressants or antipsychotics and the risk of seizure in children.

Since the first report of a possible association between psychotropic drug exposure *in utero* and childhood neurological disorders, clinicians have faced a dilemma regarding the management of women with mental disorders during both the time that they are trying to conceive and pregnancy. Ongoing efforts have been made to enhance perinatal psychiatric drug management, such as the European regulatory ban of valproate use in women of childbearing potential due to clear evidence of teratogenic and neurodevelopmental harm. However, current guidance on gestational antidepressant and antipsychotic use remains unclear due to the lack of strong clinical evidence.

When generating evidence, methodological considerations such as adequate adjustment for known confounders and increase in precision of estimates should be considered wherever possible, to minimize uncertainties of the results. Sustained efforts in ascertaining the specific benefits and harms of prenatal psychotropic medication exposure are pivotal towards individualized risk-benefit analyses of psychiatric treatment to safeguard both maternal and foetal health.

We cannot completely exclude the possibility that prenatal exposure to antidepressants or antipsychotics is related to risk for childhood seizure, but our study suggests that the association might be explained by confounding factors. Further studies stratifying antidepressants/antipsychotics by different drug classes, exposure time in different trimesters, and first-time seizure diagnosed at different developmental timepoints are needed.

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