Title:

Gestational Exposure to Antidepressants and Risk of Seizure in Offspring: A systematic review and meta-analysis.

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Abstract (166 words)

In spite of the preliminary evidence suggesting a link between gestational use of antidepressant and neurodevelopmental disorders in their offspring, the association between maternal use of antidepressants during pregnancy and the risk of neurologically-related adverse outcomes such as neonatal seizure is still unclear. This study summarises the available evidence on the association between gestational exposure to any antidepressants and the risk of seizure in neonates and children. We found that gestational antidepressant exposure is associated with a 2.3-fold higher incidence of seizure in offspring. Although a causal relationship cannot be confirmed in view of other potential confounders, our findings warrant future research on related clinical aspects, and possibly more careful monitoring of foetal neurodevelopment in pregnant women taking antidepressants during pregnancy. However, this does not suggest the abrupt withdrawal of antidepressants during pregnancy for all cases at risk of seizure in offspring as this must be balanced with the risk of negative consequences caused by untreated maternal depression, and decision-making should be individualised for each patient.

Key Words: Antidepressants, Pregnancy, Seizure, Neonates

1. Introduction

Depression is a common mental disorder that affects more than 246 million people worldwide and is characterised by persistent low mood and loss of interest, particularly in activities that were once enjoyed. It is also one of the most common complications during pregnancy, with a prevalence of around 10-20% (Dunkel Schetter and Tanner 2012). Antidepressants have been used as one of the solutions for antenatal depression with the major types of antidepressants include selective serotonin reuptake inhibitors (SSRI), serotonin and noradrenaline reuptake inhibitors (SNRI), noradrenergic reuptake inhibitors (NRI) and tricyclic antidepressants (TCA). Around 10% of women use antidepressants during pregnancy in the United States (Huybrechts et al. 2013). Antidepressants have the ability to cross both the blood-brain barrier in exerting its pharmacological actions, as well as the placental barrier, thus possibly exerting unintended actions and causing adverse consequences (Rampono et al. 2009; Kendall-Tackett and Hale 2010). Given the increasing use of antidepressants in pregnant women (Jimenez-Solem et al. 2013), it is crucial to gather more knowledge and evidence on safe use to minimise the risk of adverse effects on both the mother and foetus, and to the long-term development of the offspring.

Seizures occur most commonly during the neonatal period compared to other periods

of life, with most occurring during the first week of life (Lombroso 1996). Approximately one-third of the neonatal seizure survivors develop epilepsy(Garcias Da Silva, Nunes, and Da Costa 2004). The actual incidence of neonatal seizure is not well established, although some suggested an estimated frequency of 80-120 cases per 100,000 neonates per year(Raj D Sheth 2017).

Previous narrative review suggested an association between gestational antidepressant exposure and the risk of neonatal seizures (Uguz 2019). However, the review did not conduct a meta-analysis and also did not thoroughly evaluate different methodological issues in particular confoundings that could affect the interpretation of the apparent association of some studies. With antidepressants are still often prescribed to expecting mothers with depression (Payne and Meltzer-Brody 2009), inconsequential adverse outcomes without long-term effects on offspring can lead to unnecessary or even inappropriate cessation (Huang et al. 2017) that could lead to the deterioration of maternal psychiatric conditions and finally may cause poor delivery or neonatal outcomes.(Huang et al. 2017) In view of such a complex dilemma, we conducted a systematic review and meta-analysis on the association between antidepressant use during pregnancy and the risk of neonatal and childhood seizures.

2. Methods

Systematic Literature Search

Our systematic review and meta-analysis were reported in accordance with the MOOSE checklist (Meta-analysis for Observational Studies in Epidemiology) and the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). A systematic literature search was conducted in PubMed, PsycINFO and EMBASE up to 15 January 2020 using the following combination of search terms: (Pregnancy) AND (Antidepressants) AND (Offspring) AND ((Seizure) OR (Convulsion) OR (Epilepsy)). The complete list of search terms can be found in Appendix 1 of the supplementary material. References cited by these articles were examined and searched manually to identify additional studies. Titles and abstracts were then independently screened and reviewed by two investigators (KW and ML) to identify relevant studies. Full texts of potentially relevant papers were also retrieved to determine the eligibility of the studies. Any discrepancies were resolved in discussion between KW and ML until consensus was reached.

Inclusion and Exclusion Criteria

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. Non-English studies, animal studies, case reports, conference abstracts, book chapters, reviews and summaries were excluded. Studies only reported treated versus untreated depressed patients and did not specify that antidepressants in the treatment were also excluded, as treatment for depression may include other medications like benzodiazepines, or antipsychotics and other non-pharmacological treatment.

Quality Assessment

The Newcastle-Ottawa Scale (NOS) was adopted(Hartling L 2012; Wells 2000) to assess the methodological quality of the included studies. Two investigators (KW and ML) independently reviewed and graded each included study and any discrepancies were resolved in the discussion. A set of NOS criteria specific for case-control and cohort studies was used correspondingly. A maximum of nine scores could be assigned to each study for three areas: selection, comparability and exposure/outcome. The complete list of NOS can be found in Appendix 2 of the supplementary material. A higher score indicates a better methodological quality of the study. Studies meeting five or more of the criteria were considered of higher quality and were eligible for meta-analysis.

Data Extraction

Data extraction was then conducted using a data collection form. Data extracted included information on study characteristics (study design, data source, study period, country, sample size, inclusion and exclusion criteria, identification of cases/ exposure groups, the timing of exposure, confounders adjustment, statistical analysis) and outcomes of interest (crude numbers, incidences and adjusted estimates such as odds ratio (OR), rate ratio (RR), hazard ratio (HR) and the corresponding 95% confidence intervals (CI)). Two researchers (ML and KW) independently extracted and reviewed the data characteristics which were subsequently cross-matched to ensure accuracy and consistency.

Statistical Analysis

The primary outcome of interest was the risk of seizures or epilepsies in offspring, following gestational exposure to any antidepressants. To estimate the risk of seizure with antidepressant use during pregnancy, the results of all the included studies were pooled using DerSimonian and Laird's random-effects model(DerSimonian and Laird 1986). Higgin's I-square statistic was reported for each figure to indicate the degree of heterogeneity(DerSimonian and Laird 1986). In view of heterogeneity of meta-analysis, a sensitivity analysis was conducted by removing any studies that used different

methodology and potentially contributed to heterogeneity. Adjusted estimates were used if they were provided in the studies. The 95% Confidence intervals (CI) calculated using exact Poisson distribution were approximated using the estimate and the CI boundaries closer to 1. Estimates were calculated from crude numbers and incidences when no adjusted estimates were provided or from separate subgroup estimates when no overall estimates were provided. When only separate estimates for different antidepressants were provided, the overall estimate was calculated accordingly and used in the analysis. Sensitivity analyses were conducted using estimates for specific types of antidepressants to ensure the results were not affected by the combination.

For studies using the same database, only one estimate from the same population was included in each of the analyses. Results from studies with a higher NOS score were chosen over those with lower. Estimates with adjustments were chosen over those without, and estimates with narrower confidence intervals with larger sample sizes were chosen over those with wider. Funnel plot was used to identify the potential of publication bias and further tested by the Egger's test. Sensitivity analyses were performed by substituting estimates from studies using the same database. Sensitivity analyses were also performed using adjusted estimates alone to minimise the effects of confounders.

Studies specifically reporting exposures at early pregnancy and late pregnancy were separately examined in a subgroup analysis. Subgroup analyses were also performed by stratifying results into different types of antidepressants exposed and different follow-up periods for outcome measures. The point estimates, their 95% CIs and the plots were computed using RevMan 5.3. Test for publication bias was conducted using R (version 1.4.1717).

3. Results

Summary of systematic literature search

PubMed, PsycINFO and EMBASE were searched, yielding 807, 66 and 805 records respectively, with a total of 1678 articles, up to 15 January 2020. After removing duplicates, titles and abstracts of 1505 articles were screened. 249 articles were identified for full-text review, 233 of which were excluded as they were reviews, editorial letters, commentaries, or did not investigate the association between gestational use of antidepressants and seizures in offspring. 16 studies(Bellissima et al. 2020; Boucher, Bairam, and Beaulac-Baillargeon 2008; Cantarutti et al. 2017; Davis et al. 2007; Galbally et al. 2009; Hayes et al. 2012; Kallen 2004b; Leibovitch et al. 2013; Lennestal and Kallen 2007; Levinson-Castiel et al. 2006; Mao et al. 2016; Oberlander

et al. 2006, 2008; Simon, Cunningham, and Davis 2002; Warburton, Hertzman, and Oberlander 2010; Wen et al. 2006) were included in the review and 13 with unique data sources were included in the meta-analyses. All of the studies were published after 2000. Figure 1 shows the PRISMA flowchart for studies inclusion.

All of the studies were cohort studies. Five studies were based on medical records from a single hospital or medical center, the remaining studies were based on eight different administrative healthcare databases or registries. Five studies were conducted in Canada (Boucher, Bairam, and Beaulac-Baillargeon 2008; Oberlander et al. 2006, 2008; Warburton, Hertzman, and Oberlander 2010; Wen et al. 2006), three in the United States (Davis et al. 2007; Hayes et al. 2012; Simon, Cunningham, and Davis 2002), two in Israel (Leibovitch et al. 2013; Levinson-Castiel et al. 2006), Italy (Bellissima et al. 2020; Cantarutti et al. 2017) and Sweden, (Kallen 2004b; Lennestal and Kallen 2007) and the remaining ones in Australia (Galbally et al. 2009) and Denmark (Mao et al. 2016). The length of the recruitment period or the study period ranged from 1 year to 13 years.

Kallen et al(Kallen 2004b) and Lennestal et al(Lennestal and Kallen 2007) used the same database from Sweden. Kallen et al(Kallen 2004b) studied all types of antidepressants while Lennestal et al(Lennestal and Kallen 2007) focused on serotonin

and noradrenaline reuptake inhibitors (SNRI) and noradrenergic reuptake inhibitor (NRI) and their comparison with selective serotonin reuptake inhibitors (SSRI). Adjusted estimates from Kallen et al(Kallen 2004b) were chosen over the crude estimates of Lennestal et al(Lennestal and Kallen 2007) when conducting meta-analysis.

The three studies from the United States were also based on the same cohort(Oberlander et al. 2006, 2008; Warburton, Hertzman, and Oberlander 2010). Oberlander et al (2006)(Oberlander et al. 2006) compared mothers with serotonin reuptake inhibitors (SRI) use during pregnancy and those diagnosed with depression but without SRI use; whereas in the 2008 study(Oberlander et al. 2008), the comparison was between those who continued taking SRI till the third trimester and those who quit earlier. Warburton et al in 2010(Warburton, Hertzman, and Oberlander 2010) further focused on the comparison between those who continued and those who quit before the last 14 days of pregnancy. Oberlander et al (2006)(Oberlander et al. 2006) was included in the meta-analysis instead of the remaining two due to its larger sample size and study design being closest to that of other studies, where most of the control groups were mothers who did not use antidepressants during pregnancy. Only two other studies similarly accounted for mothers with pre-conception antidepressant use or diagnosed with depression but did not use antidepressants during pregnancy(Cantarutti et al. 2017;

Hayes et al. 2012).

All studies retrieved information on antidepressant exposure from secure medical charts(Bellissima et al. 2020; Boucher, Bairam, and Beaulac-Baillargeon 2008) or dispensing records(Cantarutti et al. 2017; Davis et al. 2007; Hayes et al. 2012; Mao et al. 2016; Oberlander et al. 2006, 2008; Simon, Cunningham, and Davis 2002; Warburton, Hertzman, and Oberlander 2010; Wen et al. 2006) except the early exposure in the two Swedish studies(Kallen 2004b; Lennestal and Kallen 2007) were obtained by structured interview by midwives at first antenatal care visit, and three studies where exposure were self-reported by mothers(Galbally et al. 2009; Leibovitch et al. 2013; Levinson-Castiel et al. 2006).

The same studies that obtained information from medical records(Bellissima et al. 2020; Boucher, Bairam, and Beaulac-Baillargeon 2008) or dispensing databases(Cantarutti et al. 2017; Davis et al. 2007; Hayes et al. 2012; Mao et al. 2016; Oberlander et al. 2006, 2008; Simon, Cunningham, and Davis 2002; Warburton, Hertzman, and Oberlander 2010; Wen et al. 2006) for exposure, also retrieved outcomes from medical records and diagnostic codes in databases respectively. The two Swedish studies(Kallen 2004b; Lennestal and Kallen 2007) used databases for diagnoses of neonatal seizure. One of

the remaining studies obtained outcome measurement from mothers' responses to a questionnaire(Galbally et al. 2009). The other two were based on nurses' or doctors' regular assessment postpartum(Leibovitch et al. 2013; Levinson-Castiel et al. 2006). While nurses' or doctors' regular assessments were required per protocol for exposed neonates, no usual care practice for unexposed neonates was reported.

To address for confounding effects, eight studies(Bellissima et al. 2020; Boucher, Bairam, and Beaulac-Baillargeon 2008; Davis et al. 2007; Galbally et al. 2009; Leibovitch et al. 2013; Levinson-Castiel et al. 2006; Simon, Cunningham, and Davis 2002; Wen et al. 2006) identified matched controls to the exposed, among which one study(Galbally et al. 2009) did not specify the matching criteria. All of them were successful in at least having one-to-one matching except for one study(Wen et al. 2006) wherein they supplemented by additional adjustment for their risk ratios reported. The studies either performed adjustment or propensity score matching for their results(Bellissima et al. 2020; Boucher, Bairam, and Beaulac-Baillargeon 2008; Cantarutti et al. 2017; Davis et al. 2007; Galbally et al. 2009; Kallen 2004b; Leibovitch et al. 2013; Levinson-Castiel et al. 2006; Mao et al. 2016; Oberlander et al. 2006; Simon, Cunningham, and Davis 2002; Warburton, Hertzman, and Oberlander 2010; Wen et al. 2006), except for three studies where they did not perform adjustment on neonatal

seizures(Hayes et al. 2012; Lennestal and Kallen 2007; Oberlander et al. 2008). Among the variables being matched or adjusted for, nine studies addressed concurrent medications(Boucher, Bairam, and Beaulac-Baillargeon 2008; Cantarutti et al. 2017; Leibovitch et al. 2013; Levinson-Castiel et al. 2006; Oberlander et al. 2006; Warburton, Hertzman, and Oberlander 2010), alcohol(Boucher, Bairam, and Beaulac-Baillargeon 2008; Leibovitch et al. 2013; Levinson-Castiel et al. 2006; Wen et al. 2006) or substance abuse(Cantarutti et al. 2017; Galbally et al. 2009; Hayes et al. 2012; Leibovitch et al. 2013; Levinson-Castiel et al. 2006; Wen et al. 2006) that may cause similar neonatal distress, eight considered maternal age(Cantarutti et al. 2017; Davis et al. 2007; Kallen 2004b; Mao et al. 2016; Oberlander et al. 2006; Simon, Cunningham, and Davis 2002; Warburton, Hertzman, and Oberlander 2010; Wen et al. 2006), five accounted for gestational age(Bellissima et al. 2020; Boucher, Bairam, and Beaulac-Baillargeon 2008; Leibovitch et al. 2013; Levinson-Castiel et al. 2006; Warburton, Hertzman, and Oberlander 2010), parity(Cantarutti et al. 2017; Hayes et al. 2012; Kallen 2004b; Mao et al. 2016; Wen et al. 2006), maternal psychiatric illnesses(Cantarutti et al. 2017; Kallen 2004b; Oberlander et al. 2006; Simon, Cunningham, and Davis 2002; Warburton, Hertzman, and Oberlander 2010) respectively, while one adjusted for parental epilepsy(Mao et al. 2016), another one adjusted for maternal epilepsy(Cantarutti et al. 2017). Details of study characteristics and quality assessment can be found in Tables 1-

2 and Appendix 3 respectively.

Syntheses of results

A total of 2,109,071 births from 13 studies across 7 countries were included in the meta-analyses(Bellissima et al. 2020; Boucher, Bairam, and Beaulac-Baillargeon 2008; Cantarutti et al. 2017; Davis et al. 2007; Galbally et al. 2009; Hayes et al. 2012; Kallen 2004b; Leibovitch et al. 2013; Levinson-Castiel et al. 2006; Mao et al. 2016; Oberlander et al. 2006; Simon, Cunningham, and Davis 2002; Wen et al. 2006). Seven studies reported a significant increase in the risk of seizures in offspring while 6 others reported no significant differences(Bellissima et al. 2020; Cantarutti et al. 2017; Davis et al. 2007; Hayes et al. 2012; Kallen 2004b; Mao et al. 2016; Wen et al. 2006). The risk of seizures was significantly higher in offspring exposed to maternal antidepressants (pooled RR, 2.30; 95% CI, 1.63-3.24) (Figure 2a). A moderate heterogeneity was found across the studies (Q statistic = 26.58, p = 0.009, I^2 = 55%) (Figure 2a). Funnel plot of the included studies was in Figure 2b. Result from the Egger's test suggested asymmetry of the funnel plot (p=0.0295). .

Another sensitivity analysis was performed using only adjusted estimates in six studies. The overall risk of seizure with adjustments was similar to that including those without

adjustments and appeared to show a slightly larger risk after adjustment but the wider confidence interval overlapped with that when all estimates were included (pooled RR, 2.42; 95% CI, 1.30-4.49) (Figure 2c).

The sensitivity analyses that substituted the overall estimates with the estimates for SSRI (pooled RR, 1.63; 95% CI, 1.42-1.87) (Figure 2d) and TCA (pooled RR, 1.61; 95% CI, 1.40-1.84) (Figure 2e), both demonstrated a similar increased risk of seizures in offspring.

Subgroup analyses

Types of antidepressants

While seven studies included all types of antidepressants in their analyses(Boucher, Bairam, and Beaulac-Baillargeon 2008; Cantarutti et al. 2017; Galbally et al. 2009; Hayes et al. 2012; Kallen 2004b; Levinson-Castiel et al. 2006; Mao et al. 2016), all the remaining studies were either specifically targeted at or separately reported SRI exposure(Bellissima et al. 2020; Davis et al. 2007; Leibovitch et al. 2013; Oberlander et al. 2006, 2008; Simon, Cunningham, and Davis 2002; Wen et al. 2006). Only one study focused on a single antidepressant(Bellissima et al. 2020), this was also the only one that investigated the association of maternal serum concentrations of the

antidepressant and a surrogate marker with neonatal outcome. Excluding those from duplicate cohorts, 10 studies reporting SRI exposure(Bellissima et al. 2020; Cantarutti et al. 2017; Davis et al. 2007; Kallen 2004b; Leibovitch et al. 2013; Levinson-Castiel et al. 2006; Mao et al. 2016; Oberlander et al. 2006; Simon, Cunningham, and Davis 2002; Wen et al. 2006) (pooled RR, 2.21; 95% CI, 1.40-3.49) (Figure 3a), within which seven studies reporting SSRI exposure(Bellissima et al. 2020; Cantarutti et al. 2017; Davis et al. 2007; Kallen 2004b; Mao et al. 2016; Simon, Cunningham, and Davis 2002; Wen et al. 2006), were compared against four studies that reported TCA exposure in subgroup analyses(Davis et al. 2007; Kallen 2004b; Mao et al. 2016; Simon, Cunningham, and Davis 2002) (pooled RR, 2.47; 95% CI, 1.37-4.44) (Figure 3b). The risk of seizures in offspring was higher in all types of antidepressants. Both subgroup analyses when comparing SSRI (Q statistic = 0.25, p = 0.62, I^2 = 0%) (Figure 3a) or SRI (Q statistic = 0.57, p = 0.45, I^2 = 0%) (Figure 3b) against TCA, did not report any significant difference.

Time period for antidepressant exposure

A substantial proportion of patients stopping antidepressants after first trimester were reported in some of the studies(Cantarutti et al. 2017; Hayes et al. 2012; Mao et al. 2016), ranging from around 30%(Hayes et al. 2012) to up to 45%(Mao et al. 2016).

Except for four studies that did not differentiate the period of exposure(Leibovitch et al. 2013; Oberlander et al. 2006; Simon, Cunningham, and Davis 2002; Wen et al. 2006), all the other studies reported estimates of specific periods in pregnancy. Most of the studies focused on the use of antidepressants during late pregnancy, investigating the hypothesis that the seizures in offspring were related to the withdrawal symptoms neonates experienced without further exposure to maternal antidepressants after birth.

Excluding duplicated cohorts, three studies reported the risk of seizures in offspring after exposure in early pregnancy during first trimester, while nine studies reported risk related to exposure in late pregnancy(Bellissima et al. 2020; Boucher, Bairam, and Beaulac-Baillargeon 2008; Cantarutti et al. 2017; Davis et al. 2007; Galbally et al. 2009; Hayes et al. 2012; Kallen 2004b; Levinson-Castiel et al. 2006; Mao et al. 2016), all including exposure during third trimester except for one expanded to the last 6 months(Bellissima et al. 2020) and another narrowed to the last three weeks(Boucher, Bairam, and Beaulac-Baillargeon 2008). Exposure in both early (pooled RR, 1.43; 95% CI, 1.08-1.88) and late (pooled RR, 2.40; 95% CI, 1.45-3.97) pregnancy both significantly increased the risk of seizure in offspring. While those exposed in late pregnancy showed a higher estimate than those exposed during early pregnancy, the difference is not statistically significant (Figure 4).

Neonatal seizures VS seizures in later life

Except for one study excluding neonatal period, the rest reported seizures in the neonatal period(Bellissima et al. 2020; Boucher, Bairam, and Beaulac-Baillargeon 2008; Cantarutti et al. 2017; Davis et al. 2007; Galbally et al. 2009; Hayes et al. 2012; Kallen 2004b; Leibovitch et al. 2013; Levinson-Castiel et al. 2006; Oberlander et al. 2006), with one extended to beyond 6 months(Simon, Cunningham, and Davis 2002) and another reviewed presence of seizures in the first year of life(Wen et al. 2006). When comparing the risk of seizures in the neonatal period only (pooled RR, 2.29; 95% CI, 1.77-2.97) against the one excluding neonatal period (pooled RR, 1.27; 95% CI, 1.06-1.54), while both were found to have significant increases in the risks, the risk during neonatal period was significantly larger than when neonatal seizures were excluded (Q statistic = 12.90, p = 0.0003, I^2 = 92.2%) (Figure 5).

Sensitivity analyses for duplicated cohorts

The results from other studies of the duplicated cohorts were substituted in meta-analysis, all synthesis of the results produced similar significant increase in risk of seizures in offspring (Supplementary Figure 1a to 1c).

4. Discussion

Our pooled results of meta-analysis of 13 studies showed that the risk of seizure in offspring with prenatal exposure to antidepressants was more than double of those unexposed. Such a significant increase was consistently found across different sensitivity analyses, regardless if Mao et al. 2016, the study that contributed most to heterogeneity, was removed, or when only adjusted estimates were synthesised, or when different estimates of the same studies or cohorts were substituted. This indicated robust evidence for the association between seizure in offspring and prenatal antidepressants use.

When separately synthesising results related to different types of antidepressants, as opposed to more side effects generally reported for TCAs in adult users, even though there is a trend of increased risk of seizure in offspring exposed to TCAs, no difference in the risk was found from those exposed to other antidepressants in general or more specifically SSRIs. TCAs with their less favourable adverse effects profile are more commonly used by patients with a longer history of depression or a more complicated depression history involving treatment failure with other antidepressants(Zahl et al. 2010). The higher risk observed with TCAs exposure may be explained by the more complicated depression more commonly found among those mothers; this is consistent

with other studies investigating the association between other neonatal outcomes with different types of antidepressants where they found no significant difference in risks of adverse outcomes across different types of antidepressants(Ray and Stowe 2014).

Most studies investigated the risk of seizures in offspring as a consequence of postpartum withdrawal of maternal antidepressants, focusing on neonatal seizures. It was hypothesised that if the increase in the risk of seizure in offspring was due to the withdrawal of residual antidepressants from the mothers, those exposed during early pregnancy should have no increased risk of seizure. However, even though the pooled estimates of those exposed in late pregnancy was significantly greater than those exposed in early pregnancy, those exposed in early pregnancy were found to have significantly increased risk as well. This indicates that the withdrawal of antidepressants in neonates may play a role in seizures in offspring, however this is only part of the explanation. The pooling of studies for early exposure was limited by the small number of studies reporting such results, among which, one study excluded the high-risk neonatal period(Mao et al. 2016) and another reported unknown proportion continued use beyond early pregnancy(Lennestal and Kallen 2007). Therefore, there still uncertainty of the risk for early exposure. More studies are needed to investigate the association between exposure in early pregnancy and the risk of seizure in offspring.

Most studies only focused on the neonatal period. When the results from the study(Mao et al. 2016) that excluded neonatal seizures were removed from the analysis, the heterogeneity dropped from medium to low (Fig 1a, 6), indicating that the neonatal period substantially affects the risk observed. This was supported in the subgroup analysis when only results from those studying neonatal period were pooled and a significantly higher risk of seizure was found, compared to those excluding neonatal period. However, the long-term seizure risk in offspring outside of neonatal period was also found to be significantly increased. This finding may suggest that the withdrawal of antidepressants in neonates may only partially explain the increase in the risk of seizures in the offspring. Due to the limited number of studies focusing beyond the neonatal period, more studies on long-term risk of seizure in offspring are needed.

A sensitivity analysis was conducted by removing Mao et al. 2016. When Mao et al was removed, the risk remained significantly higher (pooled RR, 2.28; 95% CI, 1.82-2.85), while the heterogeneity was reduced substantially (Q statistic = 11.19, p = 0.43, I^2 = 2%) (Supplementary Figure 2). The decrease in heterogeneity may be due to Mao et al excluding the neonatal period from their analyses while other studies mostly focused on the neonatal period to a maximum follow-up period of 1 year postpartum.

Proposed biological explanation

Aside from the more commonly documented and investigated withdrawal effects of antidepressants, the risk of seizure in neonates may be explained by the maternal antidepressants freely passing through the placenta, affecting neurotransmitter function and the activity of the receptors, altering foetal homeostasis and compromising long-term foetal neural development(Velasquez, Goeden, and Bonnin 2013). Exposure to antidepressants in late pregnancy may not only lead to withdrawal effects in the neonate, but may possibly lead to the increased risk of seizures in offspring beyond the neonatal period(Velasquez, Goeden, and Bonnin 2013). This could possibly be due to the direct action on foetal development that exposure to antidepressants in pregnancy has.

Potential for Confounding by Indication and Neurological Conditions

While there is a positive association between gestational use of antidepressants and risk of seizure in neonates and children, we cannot rule out the possibility that such an association may be subject to confounding by other factors, particularly familial psychiatric conditions and history of neurological conditions like epilepsy, as genetic and family history factors can also contribute to the risk of seizure in neonates and children(Panayiotopoulos 2010). This depends heavily on the study design, choice of control group and methods adopted for each study.

Cantarutti 2017 (Cantarutti et al. 2017) addressed confounding by indication by selecting women who discontinued antidepressant treatment before pregnancy as the control group. Since these subjects also have underlying depression conditions, matching for maternal psychiatric illnesses was conducted, and any confounding by indication (underlying depression) can be minimised. Similarly, Hayes et al (Hayes et al. 2012) reported three separate groups: 1) unexposed group without depression; 2) unexposed during pregnancy but with depression; 3) with depression and exposed during pregnancy. On the other hand, Oberlander et al (2008) (Oberlander et al. 2008) selected women who discontinued antidepressants during the first or second trimesters as controls. However, there still might be a discrepancy in the severity of depression between the exposed group (women using antidepressants during pregnancy) and control group as women who discontinued antidepressants before or during pregnancy are more likely to have less severe depression or be in remission, thus the complete cancellation of confounding by indication is not possible. In addition, other studies, such as Galbally 2009 (Galbally et al. 2009), defined control group as matched subjects with no antidepressants and no depression at the time of recruitment. Thus, confounding by depression was not addressed properly.

Other studies either did not mention clearly if the control group were untreated depressed mothers or healthy mothers (as they only defined the control group as pregnant women without antidepressant prescriptions), or did not match or adjust for maternal depression, other psychotropic drug use or epilepsy. Gestational age is another factor that can affect the risk of seizure in the offspring(Sun et al. 2008) and was not matched or adjusted for in two-thirds of the studies as well. All these could lead to residual confounding, with a potential biased estimate of the association between gestational antidepressant use and risk of seizure in neonates and children, thus affecting the accuracy and interpretation of the study results.

In two studies (Boucher, Bairam, and Beaulac-Baillargeon 2008; Leibovitch et al. 2013) (Levinson-Castiel et al. 2006) only neonates of women who were on antidepressants during pregnancy had a mandatory follow up time of 48 hours. However, for unexposed neonates that were reported, there was no mandatory care practice. Other studies may also have the same reporter bias of monitoring exposed neonates more regularly and vigilantly than non-exposed neonates.

Five studies took gestational age(Bellissima et al. 2020; Boucher, Bairam, and Beaulac-Baillargeon 2008; Leibovitch et al. 2013; Levinson-Castiel et al. 2006; Warburton,

Hertzman, and Oberlander 2010) into account in their analyses. However, it is likely that antidepressant use during pregnancy may affect gestational age, and thus it is likely to be a mediator rather than a confounding factor. Analyses adjusting for, matching with, stratified by mediator will lead to biased results and decrease the external validity of the study.

Clinical Implications and future studies

There has long been a dilemma over whether mothers should take antidepressants during pregnancy in consideration of their potential adverse outcomes against the risk of birth complications and adverse neonatal outcomes such as preterm birth and low birth weight caused by untreated depression(Gentile 2017). Recently, increasing attention is drawn to the possible risk of causing neurodevelopmental disorders in children (Man et al. 2015; Man et al. 2017a; Man et al. 2017b; Brown et al. 2017; Kobayashi et al. 2016; Jiang et al. 2017) in which latest evidence is suggesting that the association between prenatal antidepressant use and risk of neurodevelopmental disorders may at least partially be explained by confounding by indication of antidepressants(Man et al. 2017c; Sujan, Rickert, Öberg, et al. 2017). The current study focused on seizures, which is one of the most common neurological conditions in childhood, with the incidence of neonatal seizures in general population ranging from

0.7-2.7 per 1000 live births and the incidence of unprovoked recurrent seizures in general population ranging from 0.35-0.88 per 1000 children(Berg, Jallon, and Preux 2013). The positive association found between gestational use of antidepressants and risk of seizure in neonates and children undoubtedly warrants more future research on related clinical aspects, and possibly more careful monitoring of foetal neurodevelopment in pregnant women taking antidepressants during pregnancy and the potential long-term impact on the children or at least during the neonatal period. However, this does not suggest or encourage the abrupt withdrawal or cessation of antidepressants during pregnancy for all cases at risk of seizure in neonates and children, as this risk must be balanced with the risk of negative consequences caused by untreated maternal depression, including a higher risk of developing postpartum depression and suicidality(Andersson et al. 2004). In addition, depression during pregnancy was associated with a higher risk of preterm delivery, low birth weight and small for gestational age (SGA)(Szegda et al. 2014). Offspring development, including cognitive, behavioural, social and emotional aspects could also be potentially compromised(Bonari et al. 2004). Therefore, decision-making should be individualised for each patient.

More observational studies with better study designs are warranted to address these

potential confounding factors. Methods that address confounding by indication adopted by recent observational studies include the use of propensity score matching (Andrade 2017), sibling-matched analysis (Man et al. 2017a; Sujan, Rickert, Oberg, et al. 2017) and negative control analysis (Man et al. 2017a). Thus, future studies looking at seizure risk of gestational antidepressants might consider these methods in addressing confounding by indication.

Strengths and limitations

This systematic review and meta-analysis was conducted in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist to ensure comprehensive and standardised reporting. To ensure accuracy, consistency as well as minimal reviewer selection bias, studies have been screened, extracted and assessed by two independent research students. A predefined search strategy was also adopted with comprehensive search terms to minimise the chance of missing relevant articles. With most of the studies using administrative databases or registries as data source, huge sample size was achieved and better external validity can be ensured.

Since meta-analyses focus mainly on the effect size of the clinical outcomes, other factors, such as the methodologies and study designs that can also influence the

accuracy of estimates may not be adequately addressed. In view of this, we had adopted a widely used quality assessment tool (QAT), the Newcastle-Ottawa Scale (NOS), to evaluate the internal validity of the included studies. Some of the common limitations for case-control and cohort studies, such as inadequate follow-up period, representativeness of the sample, ascertainment of exposure, potential different characteristics of exposed and unexposed groups, imprecise measurements and adjustments of known confounders leading to residual confounding, and even unknown unaddressed confounders can be assessed by the NOS. Still, due to the small number of studies available, all studies were included in our final meta-analysis, despite the fact that one of the studies (Galbally et al. 2009) only scored 6 out of 9 stars, as shown in Appendix 3. Nevertheless, their influence on the final pooled estimate was minor due to the small effect size attributed to the small sample size and wide 95% CI.

In addition, the differences in inclusion criteria, exclusion criteria, control group definition, the time period for exposure, follow-up period, adjusted factors and statistical model among studies can also affect the accuracy of the pooled estimates. The discrepancies in storage and retrieval of pregnancy information for each study data source may explain these differences(Man et al. 2017b). We observed low to moderate heterogeneity for both crude and adjusted pooled estimates, which might be a reflection

of the differences in methodologies and analysis methods between studies. Thus, the results, especially those with medium heterogeneity, should be interpreted carefully together with professional clinical judgment. Nonetheless, the results of the forest plots of our meta-analyses are consistent with the plausible biological explanation.

Last but not least, with the limited number of studies included in our meta-analysis, a funnel plot was unable to effectively assess for publication bias. Egger's test conducted showed significant asymmetry in the funnel plot ($p=0.0295$). Thus, we cannot rule out the possibility that publication bias exists, and an overestimation of the pooled estimates might have resulted.

5. 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. Plausible biological explanations include the direct actions on the foetal brain, indirect actions through placental function disturbance, as well as the abrupt withdrawal effects of antidepressants in newborns. Confounding by co-existing depression, psychiatric illnesses and epilepsy cannot be ruled out either. The risks and benefits should be

weighed up when considering the continuation or withdrawal of antidepressants during pregnancy, and decision making ought to be individualised for each patient.

Conflict of interest:

Dr. Ip reports grants from Hong Kong Research Grants Council, Hong Kong Health and Medical Research Fund and Hong Kong Jockey Club Charities Trust, which are all outside the submitted work; Prof Wong reports grants from Hong Kong Research Grant Council. Hong Kong, personal fees from Medice, grants and personal fees from Janssen, outside the submitted work; Dr Man is the recipient of the CW Maplethorpe Fellowship; received personal fee from IQVIA Ltd., unrelated to the submitted work. Other authors declare no conflict of interests.

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. !!! INVALID CITATION !!! (Huybrechts et al. 2013).

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