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Prenatal antidepressant exposure and the risk of attention-deficit hyperactivity disorder in children: A systematic review and meta-analysis

Kenneth K.C. Man[a,b,c,d,e], Esther W. Chan[a], Patrick Ip[b], David Coghill[f,g], Emily Simonoff[h], Phyllis K.L. Chan[i], Wallis C.Y. Lau[a], Martijn J. Schuemie[j], Miriam C.J.M. Sturkenboom[d], Ian C.K. Wong[a,b,c,*]

[a] Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[b] Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[c] Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom
[d] Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands
[e] Department of Social Work and Social Administration, Faculty of Social Science, The University of Hong Kong, Hong Kong
[f] Division of Neuroscience, Medical Research Institute, University of Dundee, Dundee, United Kingdom
[g] Departments of Paediatrics and Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia
[h] King's College London, Institute of Psychiatry, Psychology and Neuroscience and NIHR Biomedical Research Centre for Mental Health, De Crespigny Park, London, United Kingdom
[i] Department of Psychiatry, Queen Mary Hospital, Hong Kong
[j] Janssen Research & Development, LLC, Titusville, NJ, United States

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ABSTRACT

This systematic review assesses the association between prenatal antidepressant exposure and risk of ADHD in children. Electronic databases were searched up to 25 July 2017. Observational studies examining this association were included in the review and meta-analysis was conducted where appropriate. Eight relevant studies were identified. The seven studies included in the meta-analysis comprised a total of 2,886,502 children. The pooled estimates comparing prenatal exposure to non-exposure showed an adjusted rate ratio (aRR) of 1.39 (95%CI 1.21–1.61). Similarly, an increased risk was found comparing previous antidepressant users and non-users: aRR = 1.56 (95%CI 1.25–1.95). The relationship between maternal psychiatric conditions and ADHD in children yielded an aRR of 1.90 (95%CI 1.47–2.45). Three studies conducted sibling-matched analyses with aRR of 0.94 (95%CI 0.75–1.16). These data suggest that the observed association between prenatal use of antidepressants and risk of ADHD in offspring can be partially explained by confounding by indication because the results from sibling-matched analyses do not support an increased risk of ADHD in discordant exposed siblings.

1. Introduction

1.1. Depression and antidepressants use in pregnancy

Females are at higher risk of developing depression than males, particularly during pregnancy (Burke et al., 2005; Yonkers et al., 2009). Untreated depression during pregnancy has been associated with poor health outcomes for both mothers and children (Sontag-Padilla et al., 2013). The decision whether to use antidepressants during pregnancy is complex and requires that both clinician and patient consider the importance of reducing depressive symptoms, and the potential for adverse events affecting mother and child. Guidelines reflect this tension and generally recommend that antidepressants should be considered for pregnant women when it is judged that the benefits will outweigh the risk (Joint Formulary Committee, 2014; National Institute for Health and Clinical Excellence, 2007).

1.2. Attention-deficit/hyperactivity disorder (ADHD) in children

ADHD is a neurodevelopmental disorder in children and adolescents characterised by pervasive hyperactivity, persistent inattention and impulsiveness, and which impairs the lives of children (American Psychiatric Association, 2013). ADHD is common among school-aged children with a worldwide prevalence of approximately 5–7%

* Corresponding author at: Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong.
E-mail address: wongick@hku.hk (I.C.K. Wong).

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(Polanczyk et al., 2014; Thomas et al., 2015). Rates of diagnosis exceed this epidemiological prevalence in North America and, whilst ADHD is under-diagnosed in most other parts of the world, rates of identified cases in other countries are increasing (Polanczyk et al., 2014). Due to the early onset, lifelong persistence, and high levels of associated co-morbidities and impairment (Karam et al., 2015), the negative impact of ADHD on social outcomes, education and health of patients and their caregivers is significant (Fleck et al., 2015).

1.3. Prenatal antidepressants exposure and the risk of ADHD in children

Recent studies have suggested a potential link between maternal prenatal exposure to antidepressants, in particular, exposure to SSRIs, and the risk of ADHD in children (Boukhris et al., 2017; Castro et al., 2016; Clements et al., 2015; Figueroa, 2010; Laugesen et al., 2013; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). Previous meta-analyses and large-scale observational studies have also reported a possible association between prenatal exposure to antidepressants and autism spectrum disorder (ASD) in offspring (Man et al., 2015; Sujan et al., 2017). Given that both ADHD and ASD are major neurodevelopmental disorders in children and are sometimes concurrent (American Psychiatric Association, 2013), this adds to the concern about treating pregnant women with antidepressants and it is therefore important to determine whether prenatal exposure to antidepressant is an inherent risk factor for ADHD.

Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed class of antidepressants, both in general, and during pregnancy. Recent meta-analyses have suggested that SSRI exposure during pregnancy is associated with preterm birth and low birth weight (Huang et al., 2014), congenital malformation (Myles et al., 2013), and persistent pulmonary hypertension (Grigoriadis et al., 2014). Antidepressants cross not only the blood-brain barrier for intended pharmacological actions but also the placental barrier, and this could have unintended consequences for the developing foetus (Kendall-Tackett and Hale, 2010; Rampono et al., 2009). Animal studies have found that transient usage of fluoxetine during early development can result in abnormal emotional behaviour in adult mice, and this suggests a potential modulation of serotonin transporters during development of the brain systems involved in emotional and stress related responses (Ansorge et al., 2004). Pharmacokinetic and pharmacodynamic data, albeit indirect and somewhat weak, suggest a plausible biological mechanism between in-utero exposure to antidepressants and ADHD in children (Ansorge et al., 2004; Kendall-Tackett and Hale, 2010; Pedersen, 2017). Antidepressants primarily target the monoamine neurotransmitters such as serotonin and norepinephrine; neuronal proliferation, migration and axonal wiring are modulated by monoamines (Pedersen, 2017). Furthermore, the use of antidepressants during pregnancy is associated with an increased risk of several birth defects and adverse birth outcomes (Grigoriadis et al., 2014; Huang et al., 2014; Louik et al., 2007; Myles et al., 2013), which may increase the risk of developing ADHD (National Institute for Health and Clinical Excellence, 2013). Placebo-controlled, randomised studies of the effects of maternal antidepressant use during pregnancy on the neurodevelopment of offspring are not feasible, and epidemiological studies therefore remain the most practical approach to investigating this association. Results from previous epidemiological studies are, however, inconsistent with contradictory findings (Boukhris et al., 2017; Castro et al., 2016; Clements et al., 2015; Figueroa, 2010; Laugesen et al., 2013; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). Evidence from most of the previous studies supports an association between prenatal antidepressant use and the risk of ADHD in children (Boukhris et al., 2017; Clements et al., 2015; Figueroa, 2010; Laugesen et al., 2013; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). However, some of these studies have emphasised that this association may be confounded by familial factors, and sibling-matched analyses do not support an increased risk (Laugesen et al., 2013; Man et al., 2017; Sujan et al., 2017). Further, those studies that used antidepressant exposure before pregnancy as a negative control also reported an increased risk for ADHD in offspring (Malm et al., 2016; Man et al., 2017; Sujan et al., 2017), suggesting that the observed increase in identified risk may have been confounded by maternal or familial factors. Given these conflicting results, it has been difficult to reach a consensus as to whether there is a link between antidepressant use in pregnancy and ADHD in children.

The possible link between prenatal antidepressant exposure and risk of neurodevelopmental disorders in childhood adds to the dilemma facing clinicians and patients in deciding how to manage severe affective disorders in women, both during pregnancy and at the time that they are trying to conceive. There can be significant unfavourable outcomes in terms of withholding or terminating antidepressant medication abruptly during pregnancy. In view of these issues, we undertook a systematic review and meta-analysis of published observational studies to evaluate the association between antidepressant exposure during pregnancy and ADHD in children.

2. Methods

2.1. Systematic literature search

A systematic literature search was conducted using the search terms in Appendix A in Supplementary material. PubMed, EMBASE, PsycINFO and Cochrane Review database were searched up to 25 July 2017. Observational studies, including cohort and case-control study designs, which investigated the association between antidepressant use in pregnancy and ADHD in children were included. In addition, sibling-matched studies that compared the exposure and outcome status among siblings born to the same mother were also included. Sibling-matched analysis can be applied in both cohort and case-control settings that compare the risk of outcome between exposed sibling(s) to non-exposed sibling(s) in cohort design; or the odds of exposure between case sibling (s) to control sibling(s) in case-control design. Case reports, animal studies and conference abstracts were excluded. English titles and abstracts were screened and full texts of relevant articles were retrieved for further review to identify relevant studies. A hand-search of selected articles was conducted to identify additional relevant studies.

2.2. Quality assessment

As recommended by the Cochrane Collaboration (Higgins and Green, 2011), the methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2000). Separate NOS criteria were used for case-control and cohort studies. A maximum of nine stars could be allocated for the following categories: selection (definition of cases/exposed subjects, representativeness of the cases/exposed subjects, selection of control/non-exposed subjects), comparability (controls or adjustment for confounding factors) and outcome/exposure (assessment/ascertainment of outcome/exposure, adequate non-response rate or follow-up time). The total score was obtained by adding the number of stars in the sub-categories where a higher score indicates better quality. Authors KM and WL independently graded all included studies using the NOS criteria.

2.3. Data extraction

Data from included studies were extracted using a standardised data collection form. Extracted data included study duration and design, data source, covariates, exposure groups, and sample size. Authors KM and WL independently extracted data and completed the characteristics form that was subsequently cross-matched to ensure consistency and accuracy. Outcome parameters such as rate ratio (RR), odds ratio (OR), hazard ratio (HR) and the corresponding 95% confidence intervals (CI) were extracted and included in the meta-analysis if appropriate. The