Antidepressants during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations

Study protocol

Literature search

A systematic review of MEDLINE and EMBASE will be performed using a pre-specified search strategy to identify all case-control, cohort or sibling studies published on or before May 2017 evaluating the risk of ASD and ADHD following antidepressant exposure during pregnancy. The search strategy will consist of the following search terms: (SSRI* OR Serotonin uptake inhibitor OR antidepressant* OR fluoxetine OR citalopram OR escitalopram OR paroxetine OR sertraline OR venlafaxine OR trazodone OR mirtazapine OR duloxetine OR amitriptyline OR nortriptyline OR imipramine OR fluvoxamine OR nefazadone) AND (pregnancy OR pregnant OR prenatal) AND (autism OR autistic OR pervasive developmental disorder OR ASD OR ADHD OR attention deficit). Titles and abstracts will be screened and full texts of relevant articles assessed for eligibility. Only English language publications and published data will be included. A cumulative review of available data (e.g. pharmacoepidemiological studies, published literature), submitted to the EMA by marketing authorisation holders of all SSRI drugs following a request by the PRAC in 2016, will be screened to identify additional studies. Methodological quality and risk of bias for the main comparison between exposed vs. unexposed women during pregnancy will be evaluated for each study using the ROBINS-I tool, including misclassification of exposure, misclassification of outcome, and selection bias. The systematic review will be reported according to PRISMA (Preferred Reporting Items for Systematic Reviews).

Data extraction

Data from included studies will be extracted for the following characteristics: study design, sample size, type of comparator or reference group reported and the accuracy and completeness of information on confounders (including the severity of depression, indication for treatment, lifestyle factors, use of co-prescribed medication, maternal age at conception and family history). For each comparison, crude and adjusted effect estimates (odds ratios, hazard ratios, rate ratios) will be identified with corresponding 95% confidence intervals. The outcomes of interest will be the risk of ASD and ADHD in children following antidepressant exposure during pregnancy.

Comparators, reference groups and sibling study design

The following pre-specified antidepressant comparator or reference groups will be extracted: 1) maternal exposure during pregnancy vs. all unexposed women; 2) maternal exposure during the pre-pregnancy period vs. all unexposed women; 3) maternal exposure during pregnancy vs. all unexposed women restricted to those with a history of affective disorder; 4) paternal exposure during the maternal pregnancy period vs. all

unexposed women; 5) effect estimates from within-family sibling analyses. Exposure windows will be as defined by the eligible studies.

Analysis

The characteristics of included studies and heterogeneity in confounding adjustment will be described. Effect estimates from each study will be used to update the results from the meta-analysis by Man et al. Crude and adjusted effect estimates will be calculated on the natural log scale and pooled using the generic inverse variance method of analysis. Random-effects models will be generated. This approach will be used to explore the other pre-specified comparisons or reference groups. Studies published using the same national data sources and patients will be included separately. Analyses will be conducted in Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).