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Abstract title: Antidepressants during pregnancy: assessing risk of autism spectrum disorders in exposed offspring using UK primary care data

Background: Several recent studies have raised the possibility of an increased risk of autism spectrum disorders (ASD) in children with an in-utero exposure to antidepressants. However, the results have been inconsistent and the possibility of confounding by indication has been acknowledged. A major limitation of previous studies is the use of secondary care data to ascertain depression despite it being overwhelmingly managed in primary care. Furthermore, the comparisons drawn in some prior studies (e.g. exposure to antidepressants versus no mental illness) are of limited clinical use as they do not directly inform the decision to initiate/continue antidepressant treatment for pregnant women with depression.

Objective: This study aimed to apply a range of traditional and advanced causal inference analytic methods including multivariable regression, propensity score matching, discordant sibling comparisons, negative controls and instrumental variable analysis to observational data on a large primary care database. We simulated two common clinical scenarios that would be tested in a randomized controlled trial: In women with depression (i) whether initiating a prescription for antidepressants in pregnancy versus offering no pharmacological treatment is associated with an increased risk of ASD in exposed offspring, and (ii) whether continuing an existing antidepressant prescription into pregnancy versus discontinuing it prior to conception is associated with an increased risk of ASD in exposed offspring.

Study Design/Methods: The Clinical Practice Research Datalink (CPRD) is an ongoing primary care database of anonymised medical records covering roughly 4.4 million active patients (6.9% of the UK population). A nested pregnancy and mother-baby register allows linkage between the clinical records of mothers and their live-born offspring. Between 1/01/1995 and 31/12/2017 we identified 46,874 mothers whose primary care records indicated depression around pregnancy, linked with 52,685 children followed up for at least 4 years. We used detailed information in the mother's clinical history prior to becoming pregnant and applied propensity score matching methods to assess severity of depression and balance the treatment groups. Children's diagnoses of ASD were identified using validated Read code lists

Results: "57.8% of depressed mothers in our study population were treated with antidepressants during pregnancy (8.5% initiated, 49.3% continued) and 42.3% were not (13.8% no treatment, 28.5% discontinued). We identified 723 children with ASD (1.37%). The results did not support any strong association between initiation of antidepressants in pregnancy and a greater risk of ASD before (OR=1.16, 95%CI 0.85-1.58) or after matching on propensity scores (OR=1.07, 95%CI 0.75-1.54). Similarly, there was little evidence to suggest that continuation of an existing prescription into pregnancy was associated with greater ASD risk before (OR=1.05, 95% CI 0.86-1.27) or after propensity score matching (OR=0.98, 95%CI 0.79-1.22)"

Conclusions: The above results suggest that for mothers with a history of depression around pregnancy, initiation or continuation of antidepressants during pregnancy did not lead to additional risk of ASD in their offspring. The results of other ongoing analyses will be presented and will provide further evidence to strengthen the causal meaning of these findings.