Antidepressants in pregnancy: applying causal epidemiological methods to understand service-use outcomes in women and long-term neurodevelopmental outcomes in exposed children

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Scientific summary

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Background

Depression is common in women of childbearing age and up to one in seven women experience depression during pregnancy. Untreated depression may have serious consequences, such as distress, self-neglect and suicidal behaviour, in affected women and birth complications in their babies. Many women with depression may, therefore, encounter a situation in which they need to decide whether to start or continue an antidepressant during their pregnancy; however, the potential for resulting harm to the neurodevelopment of their offspring is a common concern. In the absence of randomised controlled trials, the information available to guide these decisions is based on observational data, which are subject to confounding. Given that maternal depression may itself lead to adverse outcomes, isolating any effect of antidepressants from the underlying depression is particularly difficult: a problem known as confounding by indication. In the absence of randomised trials, studies designed to emulate such trials and using methods to account for confounding may help triangulate results and strengthen causal inference.

Objectives

This research aimed to simulate two scenarios that could be tested in pregnant women with depression in a hypothetical target randomised controlled trial asking the following research questions:

- Does the initiation of antidepressants for depression during pregnancy affect maternal service use outcomes and childhood neurodevelopmental outcomes?
- Does the continuation of antidepressant use during pregnancy for depression affect maternal service use outcomes and childhood neurodevelopmental outcomes?

The data were interrogated using several methods of causal inference, and assessed in relation to dose response, timing of exposure and type of antidepressants according to class and their serotonin-receptor affinity.

Methods

Design: This was an observational cohort design, with use of multiple methods to strengthen causal inference.

Setting and participants: This took place in UK general practice. Participants were UK primary care patients, specifically pregnant women with depression.

Data sources: This study used data from the Clinical Practice Research Datalink (CPRD), a large ongoing database of anonymised primary care medical records in the UK. The CPRD's pregnancy register was used to identify the dates and stages of pregnancy, and the CPRD mother–baby link allowed for the linkage of the records of pregnant women with their live born offspring. For consenting CPRD practices in England, the primary care records were linked to Hospital Episode Statistics, which include registers for inpatient admissions, outpatient care and accident and emergency (A&E) attendance in England, and with mortality data from the Office for National Statistics and Census small-area socioeconomic data.

Eligible patients: The data extract covered dates between 1 January 1995 and 31 December 2017. Within this time frame, we identified 344,720 pregnancies in the pregnancy register for which there was evidence of depressive symptoms, or prescription of an antidepressant up to 1 year before or during pregnancy. From this sample, we constructed two cohorts: (1) the pregnant women's cohort, which contained all pregnancies for which women could be followed up for at least 2 years beyond the pregnancy end date, regardless of the pregnancy outcome or ability to link to the child; (2) the mother and child cohort, which consisted of pregnancies followed up at least until delivery that could be linked with the patient records of the children arising from these pregnancies.

The pregnant women's cohort: The exclusion criteria were (1) records for which the general practice was not yet up to standard, as defined by CPRD (n = 61,704); (2) where the patient had not yet registered with her current general practice 1 year prior to conception (n = 93,638); (3) records suggesting that the woman had transferred out of the general practice while still pregnant (n = 15,627); (4) records with < 2 years' follow-up beyond the pregnancy end date (n = 18,569); (5) records that showed overlap with a preceding or successive pregnancy episode (i.e. likely recording errors, n = 23,691); (6) any successive pregnancy that started < 4 years after a prior pregnancy had ended to minimise the possibility that women were again pregnant or trying to conceive during follow-up (n = 32,930). A further 18,458 patients who had been prescribed antidepressants for indications other than depression were excluded from these analyses but were used in separate analyses comparing outcomes of antidepressant use for depression with indications other than depression. The analytic cohort included 80,103 pregnancies in 76,687 women to study women's primary care service use outcomes. Of these pregnancies, 45,358 were eligible for record linkage to study secondary care service outcomes. Among these, data on inpatient admission were available for pregnancies that had started on or after 1 April 1997 (n = 43,662); outpatient treatment data were available for pregnancies starting on or after 1 April 2003 (n = 35,674); and A&E attendance data were available for pregnancies starting on or after 1 April 2007 (n = 25,697).

The mother and child cohort: Exclusion criteria were exclusions (1), (2) and (3) described above, (4) pregnancies that showed overlap with a preceding or successive pregnancy (n = 26,357), (5) pregnancies not recorded to have resulted in a live birth (n = 72,565), (6) live deliveries that could not be linked with offspring patient records (n = 15,298), (7) pregnancies that were recorded to have lasted < 22 gestational weeks (n = 542), and (8) any offspring who transferred out of their general practice (n = 10,404) or died (n = 5) before the age of 4 years. Given that the CPRD pregnancy register includes only the first child in case of multiple deliveries, we identified an additional 546 children in the mother–baby link data set, matching on the mother's patient identification number and exact date of delivery. Setting aside mothers who had been prescribed antidepressants for indications other than depression (n = 8485) and children followed up for less than 4 years because of being born after 2013 (n = 6367), there were 34,274 children in the offspring cohort.

Treatment groups: Within each cohort, women were allocated to one of the following treatment groups: (1) women with depressive symptoms who were (i) initiated with a prescription of antidepressants during pregnancy or (ii) not initiated with antidepressant treatment during pregnancy; and (2) women already prescribed antidepressants for the treatment of depressive symptoms who (i) continued being prescribed antidepressants in pregnancy or (ii) discontinued antidepressant treatment by the start of pregnancy, as defined in the CPRD pregnancy register.

The start of follow-up was defined as the day of estimated conception, as recorded in the CPRD pregnancy register, for women who received no treatment or discontinued or continued an existing prescription, and as the date of first prescription for women who initiated an antidepressant in pregnancy. Any difference in the length of follow-up between treatment groups was accounted for in analysis.

Outcomes

Women's outcomes included general practitioner (GP) consultations (for any reason, for depression and for self-harm) and secondary care referrals made by the GP for depression or self-harm. For those with linked data, outcomes included inpatient admission for a mental health problem, outpatient attendance for a mental health problem, A&E department attendance, and all-cause and cause specific mortality. All health-care service use outcomes were assessed during pregnancy and during each of four consecutive 6-month follow-up periods after the pregnancy end date: 1–6 months, 7–12 months, 13–18 months and 19–24 months.

Child outcomes included a diagnosis of (1) autism spectrum disorder, (2) attention deficit hyperactivity disorder (ADHD) and (3) intellectual disability recorded in the GP records based on Read codes.

Analysis: In the analysis, multiple methods for confounding control were used, including multivariable regression methods, propensity score matching to account for measured confounding factors, instrumental variable analysis using prescriber preference as an instrument to account for unmeasured confounding, negative control exposures for child outcomes (discontinuation of antidepressant before pregnancy where no gestational exposure occurred), comparison of risks of outcomes across indications for antidepressants other than depression and analysis of exposure discordant pregnancies to account for confounders shared between pregnancies.

Results

Initiation versus no initiation of antidepressants for depression in pregnancy: In the women's cohort, there were 18,978 pregnancies in which women had evidence of depression during the pregnancy or in the preceding 12 months. Antidepressants were initiated in 6177 of these pregnancies. In the mother and child cohort, there were 8478 pregnancies in which women had evidence of depression and, of these, antidepressants were initiated in 2649 pregnancies.

Multivariable regression and propensity score-matched estimates suggested that women who had initiated an antidepressant consulted more frequently than women who received no antidepressants with their GPs, for any reason or specifically for depressive symptoms, during or up to 2 years after pregnancy. These women were also more likely to be still prescribed an antidepressant 2 years after the pregnancy end date [odds ratio $(OR)_{multivariableregression}$ 2.16, 95% confidence interval (CI) 1.95 to 2.39; $OR_{propensityscore}$ 2.06, 95% CI 1.82 to 2.34].

There was some evidence that offspring of mothers who initiated antidepressants had higher odds of being diagnosed with autism in propensity score-matched analyses (OR 1.64, 95% CI 1.01 to 2.66) although the CIs for this association in multivariable regression analysis crossed the null [OR 1.23 (0.85–1.78)]. There was no strong evidence for differences in odds of offspring ADHD ($OR_{multivariableregression}$ 1.48, 95% CI 0.98 to 2.24; $OR_{propensityscore}$ 1.45, 95% CI 0.87 to 2.42) or intellectual disability ($OR_{multivariableregression}$ 1.16, 95% CI 0.63 to 2.14; $OR_{propensityscore}$ 0.75, 95% CI 0.31 to 1.78) with initiation of an antidepressant during pregnancy although CIs were wide.

Continuation versus discontinuation of antidepressants: In the pregnant women's cohort, there were 61,125 pregnancies in which women had a prior prescription of antidepressants for depression and of these 37,278 women continued the antidepressant into their pregnancy while 23,847 discontinued by the start of pregnancy. In the mother and child cohort, there were 25,796 pregnancies in which women had a prior prescription of antidepressants for depression and of these 15,295 women continued the antidepressant into their pregnancy while 10,501 discontinued by the start of pregnancy.

There was consistent evidence across the main (multivariable regression and propensity score regression) and additional analyses (treatment-discordant pregnancies analysis) that women who continued antidepressants during pregnancy were more likely to have contact with health-care services at various times during and after pregnancy. These include the number of GP consultations (including consultations for depression, and self-harm), GP referrals for depression, and outpatient contacts and inpatient stays for mental health problems. Women who continued antidepressants in pregnancy were also more likely to continue to be prescribed an antidepressant 2 years following the end of pregnancy ($OR_{multivariableregression}$ 2.40, 95% CI 2.27 to 2.53; $OR_{propensityscore}$ 2.37, 95% CI 2.24 to 2.51).

There was little evidence in our regression and propensity score analyses that continuation of antidepressants into pregnancy was associated with a higher risk in the offspring of autism ($OR_{multivariableregression}$ 1.10, 95% CI 0.90 to 1.35; $OR_{propensityscore}$ 1.06, 95% CI 0.84 to 1.32), ADHD ($OR_{multivariableregression}$ 1.02, 95% CI 0.80 to 1.29; $OR_{propensityscore}$ 0.97, 95% CI 0.75 to 1.25) or intellectual disability ($OR_{multivariableregression}$ 0.81, 95% CI 0.55 to 1.19; $OR_{propensityscore}$ 0.89, 95% CI 0.61 to 1.31) as compared with discontinuing them before pregnancy. Similar results were observed in supplementary analyses including instrumental variable analyses and treatment discordant pregnancies, although these analyses were imprecise due to smaller numbers.

Results of analyses using other approaches

Instrumental variable analyses: Using prescriber preference as an instrument, we found little evidence of associations of initiation or continuation of antidepressants and any of the neurodevelopmental outcomes, although statistical power was limited.

Depression versus other indications: A higher risk of being prescribed antidepressants 2 years after pregnancy was observed when antidepressants had been initiated/continued for depressive symptoms compared with no initiation/discontinuation of antidepressants. The opposite pattern was observed (i.e., a lower risk of being prescribed antidepressants 2 years after pregnancy) when antidepressants had been initiated/continued for indications other than depression compared with no initiation/discontinuation.

Negative control analyses: There was little evidence of an association between prescription of an antidepressant for depression before pregnancy versus no prescriptions; or prescription of antidepressants during pregnancy for depression versus no prescriptions and any of the neurodevelopmental outcomes.

Timing of antidepressants: There was no consistent difference between estimates for offspring neurodevelopmental outcomes in relation to timing of initiation of antidepressants during pregnancy.

Dose response: There was some evidence for a dose response association between antidepressants prescribed to the mother in pregnancy and offspring odds of autism [ORs with 95% CIs for low, medium, and high dose respectively as compared with no antidepressant prescription: 1.19 (0.96–1.46); 1.67 (1.09–2.55); 1.75 (1.27–2.40)], although the CIs around the estimates overlapped. There was no clear evidence for dose–response association with offspring ADHD or intellectual disability.

Type of antidepressant: There was evidence of greater adjusted odds of autism among children whose mothers had been prescribed selective serotonin reuptake inhibitor (OR 1.26, 95% CI 1.04–1.53) or tricyclic antidepressants (OR 1.58, 95% CI 1.12–2.24) during pregnancy as compared with no antidepressant prescriptions. There was little evidence of similar associations for offspring ADHD or intellectual disability.

Antidepressants grouped by serotonin receptor affinity: The point estimates of offspring odds of all neurodevelopmental outcomes were lower for higher-affinity antidepressants than those for lower-affinity

antidepressants (which may often be prescribed for more severe depression) although the CIs for all estimates overlapped.

Individual antidepressants: There were variations in the estimates for neurodevelopmental outcomes in relation to individual medications but due to smaller numbers contributing to the analyses, these results should be interpreted with caution.

Conclusions

This comprehensive study of pregnant women with depression in a representative sample of UK primary care patients found that women who were initiated or continued antidepressants during pregnancy had greater service use at baseline and continued to need support with additional clinical care during pregnancy and in the 2 years following pregnancy. This was not the case for women prescribed these medications for conditions other than depression.

There was consistent evidence against any substantial risk of autism, ADHD or intellectual disability in children of women who continued versus those who discontinued antidepressants during pregnancy. Whether to continue or stop antidepressants in pregnancy is the most common clinical dilemma regarding antidepressant prescribing in pregnancy and these results should reassure women and clinicians.

There was weak and inconsistent evidence of potential associations of initiation of antidepressants during pregnancy with offspring autism which were imprecise due to smaller numbers. Further research on larger samples could help understand the robustness and causal meaning of these findings.

Limitations

Despite the large initial sample, there was limited statistical power in analyses applying several causal inference approaches and further studies in CPRD and similar samples using the approaches applied could provide further clarity and precision to our findings. There were no standard outcome measures of depression available, so we were unable to study improvements in symptoms of depression as an outcome. Finally, outcomes other than those investigated in this study may be important to women and clinicians in their decision-making process and could be investigated in future studies.

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