

Invited commentary

Prenatal exposure to selective serotonin reuptake inhibitors and autistic symptoms in young children: another red herring?[†]

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Summary

In this issue, El Marroun *et al* suggest an association between prenatal selective serotonin reuptake inhibitor (SSRI) exposure and autistic traits in children, as well as an association with prenatal depressive symptoms. However, SSRIs may be mere markers of severity of underlying illnesses and it may be premature to reach such conclusions about effects of treatment.

Studies like this raise concerns as this may fuel further anxiety and guilt among women who are faced with depression in pregnancy and possibly leave some women without treatment.

Declaration of interest

None.

We read the paper by El Marroun and colleagues¹ on prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and autistic symptoms in young children with raised concern. Autism is a severe condition that has a significant impact on children and their families. Diagnosis and identification of autism has been on the rise in the past decades.^{2,3} A number of exposures have been sought to explain this increase, with the measles, mumps and rubella (MMR) vaccine probably the most debated. However, it is now generally accepted that there is no causal link between the MMR vaccine and autism.⁴ Yet, a consequence of the well-publicised debate has been a surge in measles infections in recent years, as some parents choose not to vaccinate their children.

We still do not know the causes of autism; genetics are likely to have an impact,^{5,6} but there may indeed be more than one cause. Therefore, it is reasonable to explore various associations. With depression being common and antidepressant treatment widely used by women of childbearing age⁷ it is no surprise that antidepressants have come under the spotlight. A number of previous observational studies have sought to identify whether there may be associations between autism in children of mothers who were exposed to antidepressants in pregnancy^{8,9} and now there is this new study by El Marroun and colleagues.¹

El Marroun and colleagues' findings

El Marroun *et al* suggest an association between prenatal SSRI exposure and autistic traits in children, as well as an association between prenatal depressive symptoms without SSRI exposure.¹ However, the paper concludes that long-term drug safety trials are needed before evidence-based recommendations are possible. There is no doubt that a well-designed randomised controlled trial would be the best tool to answer the question about SSRI exposure in pregnancy and autism. Such a trial would account for both measured and unmeasured confounding and if we detect an effect, we can feel fairly certain that it is a causal effect. One question is whether it is feasible. First, if there already is some evidence that suggests harm to the unborn child, would it be ethical to conduct such a trial? Second, a trial of this kind requires a very large sample size (as autism is a relative rare outcome) and may struggle with recruitment, adherence and experience some difficulties in

following children up several years after birth. In that respect, the numbers from the study by El Marroun *et al* speak for themselves. Out of nearly 9000 eligible pregnant women, 69 received an SSRI at some point in pregnancy and these numbers rapidly dwindled when it came to the measurement of the outcome. Going through the thought process of designing a safety trial on antidepressants in pregnancy and autism it soon becomes apparent that it would be very difficult if not impossible. Nevertheless, it offers us the opportunity to explore the value of observational studies and highlight the areas where these are likely to be subject to biases.

El Marroun *et al* compare the children of a small group of women who were reported to receive SSRIs treatment in pregnancy against children of women with no exposure to SSRIs and a low score of maternal depressive symptoms. They also compare the latter group against women who were depressed, but not on antidepressants. The question is whether these are meaningful and unbiased comparisons.⁷ Table 1 in El Marroun *et al* reveals that not only do these groups differ in terms of exposure to antidepressants, but also on a range of measured covariates. For example, a quarter of the women on SSRIs were also prescribed benzodiazepines and over 50% were smoking in pregnancy. In contrast, less than 1% of the women in the non-depressed comparison group were prescribed benzodiazepines and less than 25% were smoking. A multivariable regression analysis may appear to account for some of these differences, but only for those variables that were measured and included in the analyses. We cannot ignore the fact that those who continue antidepressants in pregnancy may also be women with a history of more severe depression.

Although the paper goes to some lengths in evaluating parental reports on the outcomes there remains the possibility that the outcomes in this study are subject to reporting bias. Moreover, the absence of figures of absolute risks of autism makes it difficult for the reader to assess the numbers of children who actually experienced pervasive developmental problems. Further, if these numbers are small, the results of multivariable regression analysis can be very sensitive to misclassifications of the outcome. El Marroun *et al* suggest that their results 'demonstrated an effect of SSRIs on autistic symptoms in young children'.¹ They support this statement with evidence from animal models. However, there is an alternative interpretation of the results of this study.

[†]See pp. 95–102 and 103–104, this issue.

A different interpretation of the results

El Marroun *et al* showed that compared with children of women without depressive symptoms, in children of women with elevated depressive symptoms the odds ratio of pervasive developmental problems was 2.02 (95% CI 1.53–2.66) and the odds ratio for those prescribed SSRIs in pregnancy was 2.58 (95% CI 1.46–4.54). Indirectly, this suggests that children of women with elevated depressive symptoms and women treated with SSRIs in pregnancy were equally likely to have pervasive developmental problems (Model I, Table 2). A head-to-head comparison of the effect estimates for autistic traits of the SSRI cohort against the cohort of women with depression suggested that children of the SSRI cohort rated slightly higher on all three domains. This, however, does not prove a causal relationship between SSRI exposure in pregnancy and autistic symptoms. Rather the results may suggest that there is an association between maternal depression and childhood autistic symptoms. Hence, some animal studies have established an association between maternal stress and autism.¹⁰ Only a small proportion of women continue antidepressants in pregnancy. Thus, prescription of SSRIs in pregnancy may be a mere marker of the severity and other characteristics of the underlying depressive illnesses. Indeed, this study confirmed that the vast majority of women with depressive symptoms are left untreated in pregnancy. This may potentially pose a far greater risk to the welfare of the mother and development of the child. We fear that the proposed link between SSRIs and childhood autistic symptoms is yet another red herring with potentially detrimental consequences. It may fuel further anxiety and guilt among women, who are faced with depression in pregnancy and possibly leave some women without treatment.

Conclusions

Further research into potential associations between maternal depression and childhood autism is needed. It may be that there are certain (genetic) traits predisposing individuals to both depression and autism. A recent study of 60 000 individuals using whole genome analysis found evidence for four common genetic variants that increase risk of five different psychiatric disorders – including depression and autism.⁶ It may be the maternal depression itself (prenatal as well as postnatal) that triggers

childhood autism but let us not jump to any firm conclusions yet. Whatever the effect is, it is small even if it is real.

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