We read the paper by El Marroun and colleagues\(^1\) 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.\(^5\,6\)

We still do not know the causes of autism; genetics are likely to have an impact,\(^7\,8\) 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 age\(^7\) it is no surprise that antidepressants are associated with autistic symptoms.\(^9\) They appear to account for some of these differences, but only a small group of women might actually experience pervasive developmental problems. Further, it is difficult for the reader to assess the numbers of children who received an SSRI at some point in pregnancy and these numbers were small, the results of multivariable regression analysis can be very sensitive to misclassifications of the outcome.\(^7\) Table 1 in El Marroun and colleagues' findings\(^1\) 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, the results of multivariable regression analysis can be very sensitive to misclassifications of the outcome. El Marroun and colleagues\(^1\) 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.

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1. See pp. 95–102 and 103–104, this issue.

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**Invited commentary**

Prenatal exposure to selective serotonin reuptake inhibitors and autistic symptoms in young children: another red herring?\(^\dagger\)

Irene Petersen, Stephen Evans and Irwin Nazareth

**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.
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. 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. 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.

Irene Petersen, PhD, Department of Primary Care and Population Health, University College London, London; Stephen Evans, MSc, Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London; Irwin Nazareth, PhD, Department of Primary Care and Population Health, University College London, London, UK.

Correspondence: Irene Petersen, Department of Primary Care and Population Health, University College London, Rowland Hill Street, London NW3 2PF, UK.

Email: i.petersen@ucl.ac.uk

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