Letter to the Editors

Antidepressant use and gestational hypertension: does evidence support causality?

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We read with interest the paper by De Vera and Bérard [1] evaluating the association between antidepressant use during pregnancy and pregnancy-induced hypertension. While this study adds to a growing body of evidence surrounding such an association [2, 3], there are a number of issues that require further clarification before causation can be established.

Firstly, there may be limitations in identifying outcomes according to International Classification of Diseases (ICD-9) codes. The authors cite one validation study, which reported positive predictive values of 93% for diagnostic codes for gestational hypertension with pre-eclampsia and 84% for gestational hypertension without pre-eclampsia [1]. This study was undertaken using deliveries recorded in the Swedish Medical Birth Register during 1987–1993. A more recent study also evaluated the accuracy of ICD-9 coding for pre-eclampsia, using data from births at a US hospital during 1999–2000, reporting a lower overall positive predictive value of 54% [4]. This ranged from 45.3% for cases of mild pre-eclampsia to 84.8%, for cases of severe pre-eclampsia. Low correlation between the disease and ICD-9 codes could lead to an underestimation of reported associations, assuming the degree of correlation is not associated with the underlying disease. Importantly, and of more serious concern, is the potential for differential misclassification of outcomes, because the direction and magnitude of the bias would largely be unknown. Such differential outcome misclassification could occur if there are differences in the recording of outcomes according to additional factors that are also associated with the use of antidepressants or are directly associated with the underlying disease. For example, women using antidepressants may be more likely to visit medical practitioners and subsequently more likely to be diagnosed with gestational hypertension.

Secondly, it would be useful to have data on the type and severity of the gestational hypertension, including the proportion of women with pre-eclampsia. Toh *et al.* [3] pre-

viously identified a stronger association with prenatal selective serotonin reuptake inhibitor (SSRI) exposure and gestational hypertension with pre-eclampsia (3.91; 95% confidence interval 2.39–6.39) than with gestational hypertension without pre-eclampsia (1.61; 95% confidence interval 1.03–2.53). Whether the risk of pre-eclampsia differs from the risk of gestational hypertension without pre-eclampsia requires further clarification, but would be of clinical relevance in the management of this condition and women taking antidepressants during pregnancy. It would also contribute towards improving our understanding of the underlying mechanisms explaining associations with such outcomes.

Importantly, the management of psychiatric illness during pregnancy is extremely complex; the degree of illness can only be approximated by the presence of a prior diagnosis of depression and/or anxiety and health care utilization (i.e. psychiatrist visits) prior to pregnancy. Therefore, while adjustment for these factors may account to some degree for confounding due to underlying maternal illness, the potential for residual confounding remains. Pregnant women who continue their antidepressant therapy throughout pregnancy may differ from those who stop prior to or during the first trimester. It is noted that within both groups of cases and controls, only 32 women (7.7%) of 414 continued their antidepressant beyond the first trimester (12 weeks). Palmsten *et al.* [2] recently demonstrated that within prepregnancy antidepressant users, the relative risk for pre-eclampsia among continuers compared with discontinuers was 1.32 (95% confidence interval 0.95–1.84) for SSRIs 3.43 (95% confidence interval 1.77–6.65) for serotonin–norepinephrine reuptake inhibitors (SNRIs) and 3.26 (95% confidence interval 1.04–10.24) for tricyclic antidepressant (TCA) monotherapy. These findings either point to a direct effect of antidepressant exposure during the second/third trimester on the risks of gestational hypertension, which is in line with the proposed biological mechanism reported [1–3], or they are reflective

of differences in underlying disease pathology between continuers and discontinuers and therefore the potential for confounding by maternal illness.

We feel that given the above and, in particular, due to the difficulties involved in differentiating the underlying effects of maternal depression from that of antidepressant use, current evidence should be viewed cautiously and that it is premature to use this evidence to guide obstetric management of women with depression during pregnancy. It is important to stress the significance of adequately treating maternal psychiatric illness during pregnancy, because this may not only play an important role in the pathogenesis of gestational hypertension, but may also be associated with a range of harmful effects on maternal and offspring health.

Competing Interests

There are no competing interests to declare.

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