Letter to the Editors

Antidepressant use and gestational hypertension:
does evidence support causality? Reply letterAnick Bérard^{1,2} & Mary A. De Vera²¹Faculty of Pharmacy, University of Montreal, Montreal, QC, Canada and ²Research Center, CHU Ste-Justine, Montreal, QC, Canada,

We thank Grzeskowiak and colleagues [1] for their review of our paper published in the British Journal of Clinical Pharmacology [2]. We agree that our study adds to a growing body of evidence supporting the fact that antidepressant use during pregnancy is increasing the risk of pregnancy-induced hypertension (PIH). However, we strongly feel that further clarification of their comments is needed. Studies on the risk of medication use during pregnancy are observational in nature, and one study alone cannot determine causality; hence, our study was not designed for that purpose and was not interpreted in that way, contrary to what Grzeskowiak and colleagues [1] suggest. Causality is likely to be determined by repetition of the findings between multiple studies on the same or similar research questions. While comparing studies, however, adjusted findings, which reflect the best estimate of association between an exposure (here antidepressant) and an outcome (here PIH), taking into account potential confounders, including the indication for antidepressant use (here depression), should be used. On the contrary, Grzeskowiak and colleagues [1] have used crude estimates, hence biased estimates, to compare our findings with others, resulting in an invalid interpretation.

Adjusting for potential confounders, including the underlying indication, our study showed a 53% ($P < 0.05$) overall increase in the risk of PIH associated with antidepressant use during pregnancy, which is in line with what has been previously reported by Toh *et al.* [3] (90% increase in risk; $P < 0.05$). We acknowledge, however, that given the observational nature of our study, residual confounding can remain due to underlying maternal depression. However, Palmsten *et al.* [4] have shown that depressed women not treated with antidepressants during pregnancy were at the same risk of PIH as pregnant women who were not depressed, and that the increase in the risk of PIH was observed only amongst depressed women treated with antidepressants, leading to the conclusion that the increase in risk is probably due to the antidepressants and not the depression, contrary to what

Grzeskowiak and colleagues [1] put forward. It is true that we have no clinical data on the severity of PIH, but we have shown that the majority of cases are pregnant women with gestational hypertension. Stratifying our analyses on a subgroup of cases with pre-eclampsia would have rendered our estimates unstable, similar to what has been reported by Toh *et al.* [3].

Finally, we disagree with the argument of Grzeskowiak and colleagues [1] concerning the lack of validity of ICD-9 codes for the identification of PIH in the Quebec Pregnancy Registry. As mentioned by De Vera and Bérard [2], Ros *et al.* [5] have reported good predictive values for PIH ICD-9 diagnostic codes in the context of 'population-based' data similar to the Quebec Pregnancy Registry. On the contrary, however, Geller *et al.* [6] have reported validation estimates using data from a single hospital in the USA. One needs to be vigilant when reporting such discrepancies. Indeed, the interpretation of validation estimates of diagnostic codes needs to take into account the population setting, managed care delivery and access to care (diagnoses). The Quebec Pregnancy Registry is very similar to the Swedish Birth Register in this regard, because healthcare is universal in Quebec, and thus the Quebec Pregnancy Registry is population based (contrary to the US system), Quebec has equal access to healthcare (contrary to the USA) and Quebec has standardized prenatal follow-up regardless of underlying disease and socioeconomic status (contrary to the USA). The argument that depressed pregnant women are more likely to visit their healthcare provider and therefore obtain a diagnosis of PIH is very unlikely. Indeed, it is well known that depressed women are less likely to visit their physician during and outside of pregnancy. In addition, this argument is even less of an issue when studying an outcome that is intensely investigated during pregnancy, such as PIH, which is systematically scrutinized at every prenatal visit regardless of patient comorbidities.

In conclusion, our study was designed to assess the risk of PIH during pregnancy associated with gestational

antidepressant use and does not provide any information on benefits of antidepressant use during pregnancy. De Vera and Bérard [2] provide one more piece of information useful in the evaluation of the risks of antidepressant use during pregnancy at the patient level. Given the consistency of results between studies published thus far on this topic, it is our belief that more attention should be given to this important maternal comorbidity when prescribing antidepressants to pregnant women.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that they have obtained funding from the Canadian Institutes of Health Research for this work; authors have no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and A.B. is a consultant in the litigation involving antidepressant use during pregnancy.

REFERENCES

- 1 Grzeskowiak LE, Pederson LH, Morrison JL. Antidepressant use and gestational hypertension: does the evidence support causality? *Br J Clin Pharmacol* 2013; 75: 1373–4.
- 2 De Vera MA, Bérard A. Antidepressant use during pregnancy and the risk of pregnancy-induced hypertension. *Br J Clin Pharmacol* 2012; 74: 362–9.

- 3 Toh S, Mitchell A, Louik C, Werler MM, Chambers CD, Hernandez-Diaz S. Selective serotonin reuptake inhibitor use and risk of gestational hypertension. *Am J Psychiatry* 2009; 166: 320–8.
- 4 Palmsten K, Setoguchi S, Margulis AV, Patrick AR, Hernandez-Diaz S. Elevated risk of pre-eclampsia in pregnant women with depression: depression or antidepressants? *Am J Epidemiol* 2012; 175: 988–97.
- 5 Ros HS, Cnattingius S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. *Am J Epidemiol* 1998; 147: 1062–70.
- 6 Geller SE, Ahmed S, Brown ML, Cox SM, Rosenberg D, Kilpatrick SJ. International classification of diseases-9th revision coding for preeclampsia: how accurate is it? *Am J Obstet Gynecol* 2004; 190: 1629–33.

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