Use of domperidone and risk of ventricular arrhythmia in the postpartum period: getting to the heart of the matter

To the editor

We read with interest the study by Smolina et al investigating domperidone prescription for lactation stimulation and hospitalisation for ventricular arrhythmia.[1] There is significant controversy surrounding the use of domperidone for increasing breast milk supply, relating to both its perceived efficacy and safety, which has led to it becoming the subject of numerous reviews and debates.[2,3] In light of such controversies, it is important to have transparent and clear reporting of research findings, given their role in guiding subsequent clinical practice. This goes for any reporting of benefits or risks associated with the use of domperidone. We believe that the conclusion reached by Smolina *et al.* that they "found a possible association between exposure to domperidone and hospitalisation for ventricular arrhythmia among a cohort of women who have recently given birth",[1] does not accurately represent the entirety of the data upon which the conclusion is based due to the following three issues.

The first issue relates to reporting effect measure modification of the association between domperidone and ventricular arrhythmia by previous history of ventricular arrhythmia. The authors comment on the lack of ability to investigate an interaction between domperidone exposure and history ventricular arrhythmia due to the fact that all 6 women exposed to domperidone and hospitalised for ventricular arrhythmia also had a history of ventricular arrhythmia. Visual inspection of the data (Table 1) points to effect measure modification by history of ventricular arrhythmia. In the stratum of women who have no history of ventricular arrhythmia (n=318,516), there were no ventricular arrhythmia events among the 45,163 women prescribed domperidone, and all ventricular arrhythmia events arose in women who were not prescribed domperidone. Different results are obtained by looking across stratum of ventricular arrhythmia history; negligible risk among women with no ventricular arrhythmia history and some increased level of risk among history of ventricular arrhythmia but there are too few cases to estimate with accuracy. Drawing conclusions from the pooled data hides the fact that the burden of risk is in the group of women with ventricular arrhythmia

history. A more balanced interpretation might be that use of domperidone is associated with an increased risk of ventricular arrhythmia among women with a previous history of ventricular arrhythmia, but not among those with no ventricular arrhythmia history. The conclusion reached by the study authors does not reflect this differential risk and has potential to reduce domperidone prescriptions and lactation success for all women, irrespective of their history. Therefore, we ask that the adjusted stratum-specific hazard ratios be presented separately according to ventricular arrhythmia history.

The second issue relates to the potential for significant residual confounding of the association between domperidone exposure and hospitalisation for ventricular arrhythmia in women with a previous history of ventricular arrhythmia. Confounding appears to be a significant factor, as evidenced by the change in the overall risk estimate when accounting for maternal body mass index, for which complete data was notably absent. The approach undertaken for confounder selection is not entirely clear, with the inclusion of only some cardiovascular risk factors such as smoking as confounders while other factors such as thyroid dysfunction, diabetes and hypertension (whether pre-existing or pregnancy induced) are omitted. Further, preterm birth or neonatal hospitalisation are potential confounders, as both of these are strongly associated with domperidone use[4-6] and can lead to significant physical and emotional stress during the post-partum period, the latter of which is a noted factor influencing rhythm disorders among some women.[7] While it is appreciated that the number of covariates was limited to avoid over-fitting the model, the authors could consider use of alternative propensity score methodology which has demonstrated robustness in the setting of large numbers of potential confounders relative to uncommon outcomes.[8]

The third issue relates to the manner in which domperidone exposure was classified and included in the analyses. It is noted that of the six women exposed to domperidone who were hospitalised for ventricular arrhythmia, only four had a current domperidone prescription at the time of hospitalisation. This aspect requires clarification as it is unclear why women would continue to be treated as exposed until 30 days after the day that the last postpartum domperidone prescription would

have run out, when based on a biological half-life of 7.5 hours[9], domperidone would take less than 48 hours to be cleared from the body after the final dose has been taken.

In light of the findings of the study by Smolina *et al.*, we feel that a more appropriate summary for clinicians and lactating mothers considering the use of domperidone would be: Among mothers with no previous history of ventricular arrhythmia, no increased risk was observed between the use of domperidone and risk of subsequent ventricular arrhythmia. In contrast, in mothers with a previous history of ventricular arrhythmia, the use of domperidone may be associated with a small absolute increase in the risk (1.7 to 2.3 fold based on adjusted hazard ratio) of subsequent ventricular arrhythmia (an absolute increase from 68 cases per 10,000 women to 115-157 cases per 10,000 women). Therefore, use of domperidone in women with a previous history of ventricular arrhythmia should be cautioned and only undertaken under careful supervision. Overall, domperidone should only be considered after a careful evaluation of the anticipated benefits and risks for each individual mother-child pair and should never be seen as a replacement for non-pharmacological strategies for increasing breast milk supply.

Conflict of Interest:

The authors have indicated that they have no financial relationships or conflicts of interest relevant to this article to disclose.

References

1. Smolina K, Mintzes B, Hanley GE, Oberlander TF, Morgan SG. The association between domperidone and ventricular arrhythmia in the postpartum period. *Pharmacoepidemiol Drug Saf* 2016; DOI: 10.1002/pds.4035

2. Paul C, Zénut M, Dorut A, et al. Use of domperidone as a galactagogue drug a systematic review of the benefit-risk ratio. *J Hum Lact* 2015; 31(1):57-63. DOI: 10.1177/0890334414561265.

3. Grzeskowiak LE, Amir LH. Pharmacological management of low milk supply with domperidone: separating fact from fiction. *Med J Aust* 2014;201(5):257-258. DOI: 10.5694/mja14.00626

4. Grzeskowiak LE, Lim SW, Thomas AE, Ritchie U, Gordon AL. Audit of domperidone use as a galactogogue at an Australian tertiary teaching hospital. *J Hum Lact* 2013;29(1):32-37. DOI: 10.1177/0890334412459804

5. Smolina K, Morgan S, Hanley GE, Oberlander TF, Mintzes B. Large increase in domperidone use postpartum in British Columbia: a retrospective cohort study. *CMAJ Open* 2015; 4: E13–E19. DOI:10.9778/cmajo.20150067

6. Grzeskowiak LE, Dalton JA, Fielder AL. Factors associated with domperidone use as a galactogogue at an Australian tertiary teaching hospital. *J Hum Lact* 2015;31(2):249-53. DOI: 10.1177/0890334414557175

7. Rashba EJ, Zareba W, Moss AJ, Hall WJ, Robinson J, Locati EH, Schwartz PJ, Andrews M, LQTS Investigators. Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome. *Circulation* 1998 10;97(5):451-6. DOI: 10.1161/01.CIR.97.5.451

8. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol* 2003;158:280–7. DOI: 10.1093/aje/kwg115

9. Heykants J, Hendriks R, Meuldermans W, Michiels M, Scheygrond H, Reyntjens H. On the pharmacokinetics of domperidone in animals and man IV. The pharmacokinetics of intravenous domperidone and its bioavailability in man following intramuscular, oral and rectal administration. *Eur J Drug Metab Pharmacokinet* 1981; 6(1):61-70. DOI: 10.1007/BF03189516

Table 1. Numbers of women exposed and not exposed to domperidone in the postpartum period and subsequent development of ventricular arrhythmia			
Overall Cohort			
	VA	**No VA**	**Total**
Domperidone	6	45,512	45,518
No Domperidone	15	274,818	274,833
Stratified According to History of Ventricular Arrythmia (VA)			
Previous History of VA			
	VA	**No VA**	**Total**
Domperidone	6	349	355
No Domperidone	10	1,470	1,480
No History of VA			
	VA	**No VA**	**Total**
Domperidone	0	45,163	45,163
No Domperidone	5	273,348	273,353