Diclectin for morning sickness

Long-term neurodevelopment

Irena Nulman MD FRCPC **Gideon Koren** MD FRCPC FACMT

Abstract

Question A pregnant patient recently asked me whether using Diclectin for morning sickness might affect the development of her child.

Answer Our recent large study does show such a trend, although the differences are not necessarily clinically significant.

Résumé

Question Une de mes patientes enceintes m'a demandé si l'utilisation du Diclectin pour les nausées matinales pourrait nuire au développement de son enfant.

Réponse Selon notre importante étude récente, il y a une telle tendance, mais les différences ne sont pas nécessairement significatives sur le plan clinique.

Nausea and vomiting of pregnancy (NVP) is exhibited in 80% of pregnancies, with symptoms peaking between 5 and 12 weeks' gestation.[1] Nausea and vomiting of pregnancy might have adverse effects on women's health.[2-3] In Canada, the only approved antiemetic drug for use in pregnancy is Diclectin, which is a combination of 10 mg of doxylamine and 10 mg of vitamin B6 in a delayed-release formulation.

In contrast to maternal health, NVP is associated with favourable fetal outcomes, including reduced rates of miscarriage, stillbirth, preterm birth, intrauterine growth retardation, and congenital malformations.[4-9] Although these findings suggest an early protective benefit of NVP, the effects of NVP on long-term child neurodevelopment, particularly intelligence and specific cognitive skills, have not been appropriately investigated.

Motherisk study

We designed a study to assess the neurodevelopment of children exposed to maternal use of Diclectin, as well as the effect of NVP, with formal standardized tests.[10] Of the 92 women with NVP who were studied, 40 experienced NVP only during the first trimester, 29 during the second trimester, and 23 during the third trimester. Significantly more women in the Diclectin-treated group had longer-lasting NVP than women choosing not to treat their condition ($P<.02$).

Children from the NVP-with-Diclectin group scored significantly higher on measures of IQ than children in the no-Diclectin and no-NVP groups. Children from the no-NVP group scored significantly ($P<.003$) lower on NEPSY (a developmental NEuroPSYchological assessment) Verbal Fluency than children from both NVP groups (with or without Diclectin). Similarly, children in the no-NVP group scored lower than children in the NVP groups (with and without Diclectin) on the McCarthy numerical memory forward test ($P<.004$). On the NEPSY Phonological Processing test, children in the no-NVP group scored significantly lower ($P<.004$) than children in the NVP-with-Diclectin group. However, there was no difference in NEPSY Phonological Processing scores between the NVP-without-Diclectin group and the no-NVP group. Additionally, no differences in full-scale IQ assessed with the Wechsler abbreviated scale of intelligence were found among mothers in the 3 groups.

With regression analysis, adjusted for a child's age and sex, the severity of NVP and group affiliation were both revealed to be significant predictors for all 5 psychological outcomes. Analyses revealed the NVP group had significantly higher scores than the no-NVP group on 4 indices.

We assessed the direct effect of NVP on a child's neurodevelopment. Results revealed that children of women with NVP had significantly higher nonverbal intelligence scores (ie, performance IQ) than children whose mothers did not have NVP; however, they had similar verbal intelligence scores to children whose mothers did not have NVP. We found that 21% of the children exposed to NVP (vs 7% of children not exposed) had scores of 130 or higher, which is 2 SD higher than the population mean (100 [SD 15]). Children exposed to NVP also scored higher than children not exposed to NVP on verbal processing and forward digit span measures and showed a non-significant trend toward better

expressive and receptive language skills and better visuomotor skills.

A possible mechanism that might account for the association observed between NVP and improved performance in the offspring is the variation in the maternal hormonal milieu during pregnancy, especially maternal levels of estradiol and prolactin that might positively affect neurogenesis in the fetal brain; offspring exposed to higher levels could develop enhanced neural capabilities. Because children of women with more NVP are exposed to higher levels of such hormones during gestation, they might experience better outcomes. The relatively broad age range of the children was chosen to be close in time to pregnancy but still allow the children to be old enough that we could sample a range of abilities and behaviour, as well as to ensure an adequate sample size within the study time frame.

Conclusion

These results of this Motherisk study[10] suggest a positive association between child neurodevelopment and severity of NVP, with no adverse effects of Diclectin treatment for its symptoms. Nausea and vomiting of pregnancy is a widespread and puzzling physiological phenomenon, which has yet to be sufficiently studied. The results emphasize the need for further scientific investigation into the physiological basis of NVP in order to provide safer management and more successful pregnancy outcomes in the future.

Competing interests
The study was supported by Duchesnay Inc in Blainville, Que.

References
1. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. *Br J Gen Pract* 1993;43(371):245-8.
2. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. *N Eng J Med* 1998;338(16):1128-37.
3. Einarson A, Maltepe C, Boskovic R, Koren G. Treatment of nausea and vomiting in pregnancy: an updated algorithm. *Can Fam Physician* 2007;53:2109-11.
4. Czeizel AE, Puhó E. Assocation between severe nausea and vomiting in pregnancy and lower rates of preterm births. *Paediatr Perinat Epidemiol* 2004;18(4):253-9.
5. O'Brien B, Naber S. Nausea and vomiting during pregnancy: effects on the quality of women's lives. *Birth* 1992;19(3):138-43.
6. Tierson FD, Olsen CL, Hook EB. Nausea and vomiting of pregnancy and association with pregnancy outcome. *Am J Obstet Gynecol* 1986;155(5):1017-22. Erratum in: *Am J Obstet Gynecol* 1989;160(2):518-9.
7. Boneva RS, Morre CA, Botto L, Wong LY, Erickson ID. Nausea during pregnancy and congenital heart defects: a population-based case-control study. *Am J Epidemiol* 1999;149(8):717-25.
8. Weigel MM, Reyes M, Caiza ME, Tello N, Castro NP, Cespedes S, et al. Is the nausea and vomiting of early pregnancy really feto-protective? *J Perinat Med* 2006;34(2):115-22.
9. Sherman PW, Flaxman SM. Nausea and vomiting in an evolutionary perspective. *Am J Obstet Gynecol* 2002;186(5 Suppl Understanding):S190-7.
10. Nulman I, Rovet J, Barrera M, Knittel-Keren D, Feldman BM, Koren G. Long-term neurodevelopment of children exposed to maternal nausea and vomiting of pregnancy and Diclectin. *J Pediatr* 2009;155(1):45-50, 50.e1-2. Epub 2009 Apr 24.

MOTHERISK Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Dr Nulman** is Associate Director and **Dr Koren** is Director of the Motherisk Program. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation. He holds the Ivey Chair in Molecular Toxicology in the Department of Medicine at the University of Western Ontario in London.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future **Motherisk Updates**.

Published **Motherisk Updates** are available on the *Canadian Family Physician* website (**www.cfp.ca**) and also on the Motherisk website (**www.motherisk.org**).